SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: MARCELA M CORDERO GARCIA Examiner #: 80381 Date: 11/16/04
Art Unit: 1654 Phone Number 3P 2 2939 Serial Number: PCT US04/04494
Mail Box and Bldg/Room Location: REM 3C18 3C35 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. RELATED CASE TO 10/780,5

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract

Title of Invention: ANTI-ANGIOGENIC AND ANTI-TUMORAL PROPERTIES OF BETA AND GAMMA SECRETASE INHIBITOR

Inventors (please provide full names): PARIS, DANIEL; MULLAN, MICHAEL, J.; JOHNSON, BARBARA E.

Earliest Priority Filing Date: 2/18/2003 (FEB. 18. 2003)

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

PLEASE SEARCH:

CLAIM 1 AND CLAIM 4 (STRUCTURE).

SPEC PAGES ATTACHED FOR KEYWORDS.

THANKS,

Marcela M Cordero Garcia

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Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed:	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

PTO-1590 (8-01)

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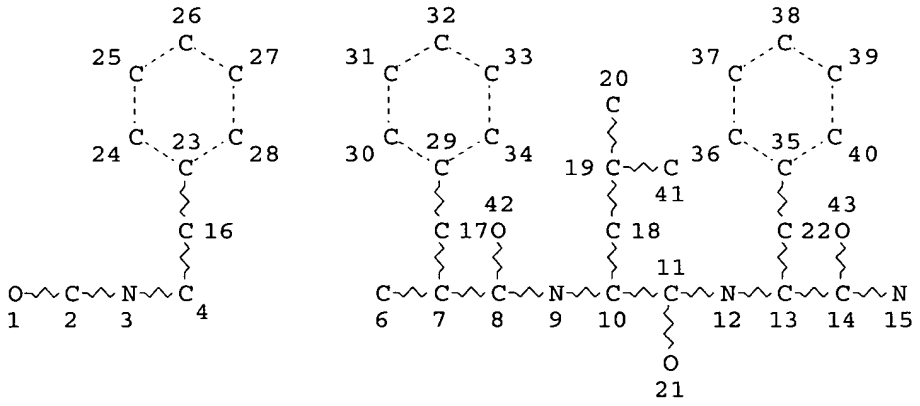
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FILE LAST UPDATED: 28 Nov 2004  (20041128/ED)

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NUMBER OF NODES IS  42

STEREO ATTRIBUTES: NONE
L2            59 SEA FILE=REGISTRY SSS FUL L1
L3            38 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2
L5            33 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND PY<=2003
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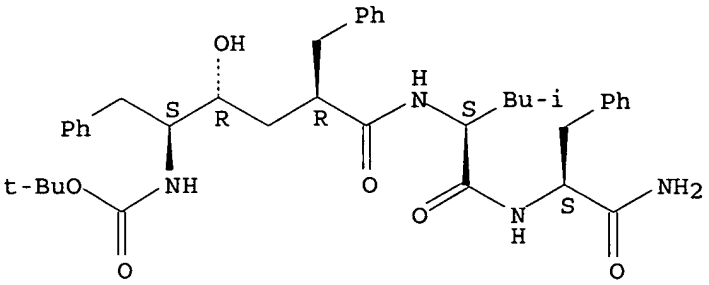
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L5 ANSWER 1 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:579517 HCAPLUS
DOCUMENT NUMBER: 139:272774
TITLE: The Mechanism of γ-Secretase: Multiple Inhibitor Binding Sites for Transition State Analogs and Small Molecule Inhibitors
AUTHOR(S): Tian, Gaochao; Ghanekar, Smita V.; Aharony, David; Shenvi, Ashok B.; Jacobs, Robert T.; Liu, Xiaodong; Greenberg, Barry D.
CORPORATE SOURCE: Department of Lead Discovery, AstraZeneca Pharmaceuticals, Wilmington, DE, 19850, USA
SOURCE: Journal of Biological Chemistry (**2003**), 278(31), 28968-28975
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Transition state analogs pepstatin Me ester (PME) and L685458 have been shown to inhibit γ-secretase non-competitively (Tian, G., Sobotka-Briner, C., Zysk, J., Liu, X., Birr, C., Sylvester, M. A., Edwards, P. D., Scott, C. W., and Greenberg, B. D. (2002) J. Biol. Chemical 277, 31499-31505). This unusual kinetics suggests phys. separation of the sites for substrate binding and catalysis with binding of the transition state analogs to the catalytic site and not to the substrate binding site. Methods of inhibitor cross-competition kinetics and competition ligand binding were utilized to address whether non-transition state small mol. inhibitors, which also display non-competitive inhibition of γ-secretase, inhibit the enzyme by binding to the catalytic site as well. Inhibitor cross-competition kinetics indicated competitive binding between the transition state analogs PME and L685458 and between small mol. arylsulfonamides and benzodiazepines, but non-competitive binding between the transition state analogs and the small mol. inhibitors. These results were indicative of two inhibitor binding sites, one for transition state analogs and the other for non-transition state small mol. inhibitors. The presence of two inhibitor binding sites for two different classes of inhibitors was corroborated by results from competition ligand binding using [3H]L685458 as the radioligand. Although L685458 and PME displaced the radioligand at the same concns. as for enzyme inhibition, arylsulfonamides and benzodiazepines did not displace the radioligand at their Ki values, a result consistent with the presence of two inhibitor binding sites. These findings provide useful insights into the catalytic and regulatory mechanisms of γ-secretase that may facilitate the design of novel γ-secretase inhibitors.

IT **292632-98-5**, L685458
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor cross-competition kinetic anal. indicates γ-secretase has sep. binding sites for transition state isosteres and for small mol. inhibitors)
RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

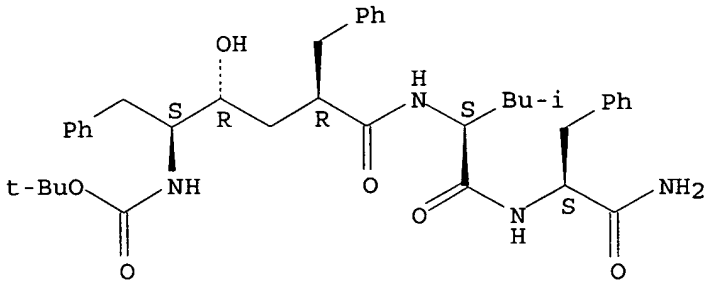
L5 ANSWER 2 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:469486 HCAPLUS
DOCUMENT NUMBER: 139:161400
TITLE: In vitro characterization of the presenilin-dependent γ-secretase complex using a novel affinity ligand
AUTHOR(S): Beher, Dirk; Fricker, Michael; Nadin, Alan; Clarke, Earl E.; Wrigley, Jonathan D. J.; Li, Yue-Ming; Culvenor, Janetta G.; Masters, Colin L.; Harrison, Timothy; Shearman, Mark S.
CORPORATE SOURCE: Departments of Biochemistry & Molecular Biology and Medicinal Chemistry, The Neuroscience Research Centre, Merck Sharp Dohme Research Laboratories, Harlow/ Essex, CM20 2QR, UK
SOURCE: Biochemistry (**2003**), 42(27), 8133-8142
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:161400

AB γ-Secretase is the enzyme activity releasing the amyloid-β peptide from membrane-bound processing intermediates derived from the β-amyloid precursor protein. Cellular release and subsequent aggregation of the amyloid-β peptide is thought to be causative for the pathogenesis of Alzheimer's disease. γ-Secretase performs an unusual intramembranous cleavage and has been closely linked to a macromol. complex containing presenilins. To generate a mol. probe for γ-secretase, the authors have developed a novel biotinylated affinity ligand which is based on a specific inhibitor containing a hydroxyethylene dipeptide isostere, known to serve as a transition state analog for aspartic proteinases. Using this probe the authors confirmed the presence of the presenilin heterodimer and mature nicastrin in the active enzyme complex and, furthermore, that substrate binding site(s) and active center(s) are spatially separated Affinity pptns. suggest that only a discrete fraction of cellular presenilin is present in the active γ-secretase complex and that both γ(40)- and γ(42)-activities are mediated by the same mol. entity. This was also reflected by a co-distribution of both enzyme activities in subcellular fractions enriched for trans-Golgi network membranes.

IT **292632-98-5**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of biotinylated affinity ligand and characterization of presenilin/nicastrin-dependent γ-secretase complex)
RN 292632-98-5 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



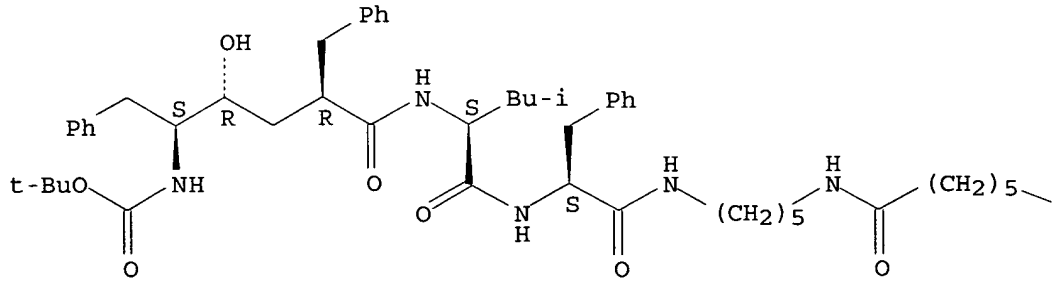
IT **392658-39-8P 392658-40-1P**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of biotinylated affinity ligand and characterization of presenilin/nicastrin-dependent γ-secretase complex)

RN 392658-39-8 HCAPLUS

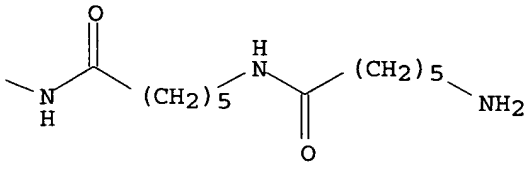
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[6-[[6-[(6-amino-1-oxohexyl)amino]-1-oxohexyl]amino]-1-oxohexyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



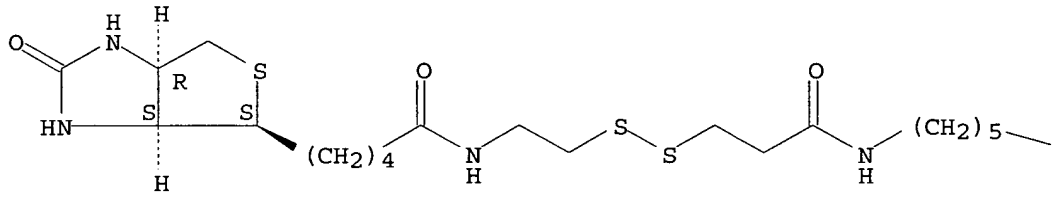
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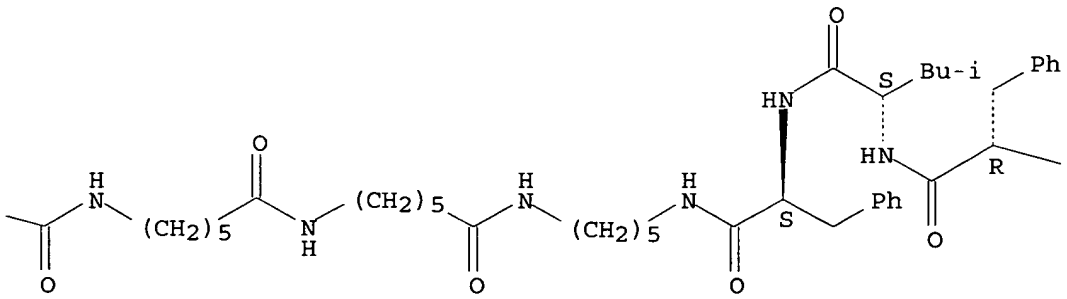
RN 392658-40-1 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[40-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-7,14,21,28,36-pentaoxo-31,32-dithia-6,13,20,27,35-pentaazatetracont-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

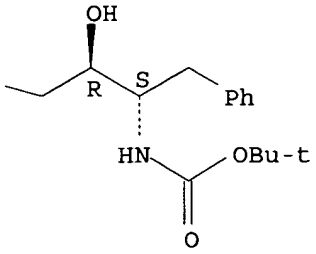
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PAGE 1-B



PAGE 1-C



REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:459131 HCAPLUS
DOCUMENT NUMBER: 139:242142
TITLE: Presenilin-1 and Presenilin-2 Exhibit Distinct yet Overlapping γ-Secretase Activities
AUTHOR(S): Lai, Ming-Tain; Chen, Elizabeth; Crouthamel, Ming-Chih; DiMuzio-Mower, Jillian; Xu, Min; Huang, Qian; Price, Eric; Register, R. Bruce; Shi, Xiao-Ping; Donoviel, Dorit B.; Bernstein, Alan; Hazuda, Daria; Gardell, Stephen J.; Li, Yue-Ming
CORPORATE SOURCE: Department of Biological Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Journal of Biological Chemistry (**2003**), 278(25), 22475-22481
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Presenilin-1 (PS1) and presenilin 2 (PS2) are proposed to be transmembrane aspartyl proteases that cleave amyloid precursor protein and Notch. PS1- and PS2-mediated activities were individually characterized using blastocyst-derived (BD) cells and membranes from PS1+/--PS2-/- and PS1-/-PS2+/+ mice, resp. The relative amts. of PS1 and PS2 in the various BD cells were determined from the intensities of the anti-PS1 and anti-PS2 immunoblot signals by comparison with standard curves using radiolabeled PS1 and PS2 stds. produced by in vitro transcription and translation. Cellular membranes from wild type, PS1-/-PS2+/+, and PS1+/--PS2-/- but not PS1-/-PS2-/- BD cells generated the Aβ40 and Aβ42 products from the C100FLAG substrate. PS1-associated γ-secretase displays considerably higher specific activity than PS2-associated γ-secretase. Moreover, the PS1+/-PS2-/- BD cells and corresponding membranes exhibited much higher γ-secretase activity as compared with other BD cells and membranes. The PS1-mediated γ-secretase activity correlated better with the amount of PS1 that is modifiable by a photoactivated active site-directed γ-secretase inhibitor rather than total PS1; hence, only a small portion (<14%) of the PS1 in wild-type membranes appears to be engaged in an active γ-secretase complex. This finding suggests that PS1 may serve other biol. functions in addition to that associated with its γ-secretase activity. Furthermore, the PS1 γ-secretase

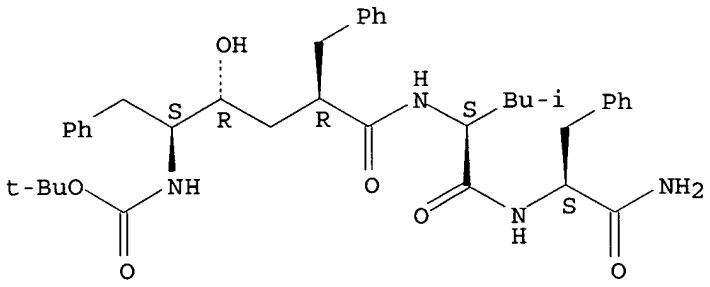
complex and the PS2 γ-secretase complex activities can be discriminated on the basis of their susceptibility to inhibition by a potent γ-secretase inhibitor. The distinct yet overlapping enzymic properties of the PS1 γ-secretase complex and the PS2 γ-secretase complex imply that these two putative aspartyl class proteases may contribute to different biol. processes.

IT **292632-98-5**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(presenilin-1 and presenilin-2 exhibit distinct yet overlapping γ-secretase activities)

RN 292632-98-5 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:415932 HCAPLUS
DOCUMENT NUMBER: 139:127922
TITLE: Catalytic Site-Directed γ-Secretase Complex Inhibitors Do Not Discriminate Pharmacologically between Notch S3 and β-APP Cleavages
AUTHOR(S): Lewis, Huw D.; Perez Revuelta, Blanca I. Perez; Nadin, Alan; Neduvelil, Joe G.; Harrison, Timothy; Pollack, Scott J.; Shearman, Mark S.
CORPORATE SOURCE: Departments of Biochemistry and Molecular Biology and Medicinal Chemistry, The Neuroscience Research Centre, Merck Sharp Dohme Research Laboratories, Harlow Essex, CM20 2QR, UK
SOURCE: Biochemistry (**2003**), 42(24), 7580-7586
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The generation of γ-secretase inhibitors which block the release of β-amyloid peptide (Aβ) has long been an attractive therapeutic avenue for treatment or prevention of Alzheimer's disease (AD). Such inhibitors would reduce levels of Aβ available for aggregation into toxic assemblies that lead to the plaque pathol. found in affected brain tissue. Cumulative evidence suggests that the S3 cleavage of Notch is also dependent on presenilins (PS) and is carried out by the multimeric PS-containing γ-secretase complex. It is therefore possible that Notch function could be affected by γ-secretase inhibitors. To assess the relation between the cleavage of these substrates in the same system,

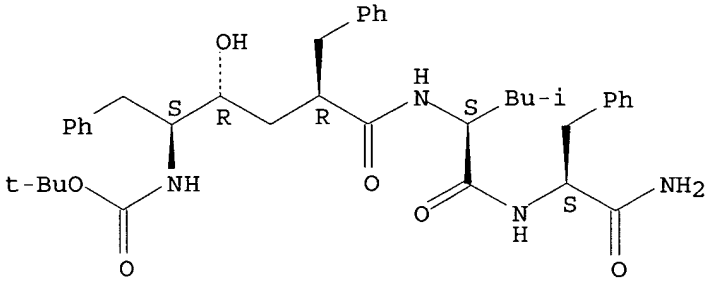
Western blot cleavage assays have been established using a human cell line stably expressing both the β-amyloid precursor protein (β-APP) and the truncated Notch1 receptor fragment NotchΔE. Thus, a direct correlation may be made, following inhibitor treatment, of the decrease in the levels of the cleavage products, Aβ peptide and the Notch intracellular domain (NICD), as well as the increase in stabilized levels of both substrates. This anal. has been performed with a range of selected γ-secretase inhibitors from six distinct structural classes. Changes in all four species usually occur in concert and with remarkably good agreement. A significant cleavage window is not clearly apparent in any case. Thus, these Notch and β-APP cleavages cannot be dissected apart easily since they show the same pharmacol. profile of inhibition. Whether this translates into proportionally reduced Notch signaling in vivo, however, remains to be seen.

IT **292632-98-5**, L-685458
RL: PAC (Pharmacological activity); BIOL (Biological study)
(catalytic site-directed γ-secretase complex inhibitors do not discriminate pharmacol. between Notch S3 and β-APP cleavages)

RN 292632-98-5 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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L5 ANSWER 5 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:346420 HCAPLUS
DOCUMENT NUMBER: 139:159884
TITLE: Targeting Presenilin-type Aspartic Protease Signal Peptide Peptidase with γ-Secretase Inhibitors
AUTHOR(S): Weihofen, Andreas; Lemberg, Marius K.; Friedmann, Elena; Rueeger, Heinrich; Schmitz, Albert; Paganetti, Paolo; Rovelli, Giorgio; Martoglio, Bruno
CORPORATE SOURCE: Institute of Biochemistry, Swiss Federal Institute of Technology (ETH), ETH-Hoenggerberg, Zurich, 8093, Switz.
SOURCE: Journal of Biological Chemistry (**2003**), 278(19), 16528-16533
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Presenilin is implicated in the pathogenesis of Alzheimer's disease. It is thought to constitute the catalytic subunit of the γ-secretase

complex that catalyzes intramembrane cleavage of β-amyloid precursor protein, the last step in the generation of amyloidogenic Aβ peptides. The latter are major constituents of amyloid plaques in the brain of Alzheimer's disease patients. Inhibitors of γ-secretase are considered potential therapeutics for the treatment of this disease because they prevent production of Aβ peptides. Recently, the authors discovered a family of presenilin-type aspartic proteases. The founding member, signal peptide peptidase, catalyzes intramembrane cleavage of distinct signal peptides in the endoplasmic reticulum membrane of animals. In humans, the protease plays a crucial role in the immune system. Moreover, it is exploited by the hepatitis C virus for the processing of the structural components of the virion and hence is an attractive target for anti-infective intervention. Signal peptide peptidase and presenilin share identical active site motifs and both catalyze intramembrane proteolysis. These common features let the authors speculate that γ-secretase inhibitors directed against presenilin may also inhibit signal peptide peptidase. Here the authors demonstrate that some of the most potent known γ-secretase inhibitors efficiently inhibit signal peptide peptidase. However, the authors found compds. that showed higher specificity for one or the other protease. The authors findings highlight the possibility of developing selective inhibitors aimed at reducing Aβ generation without affecting other intramembrane-cleaving aspartic proteases.

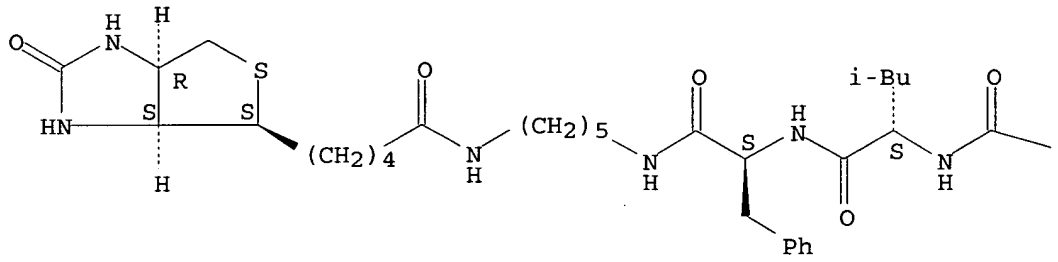
IT **288290-55-1**, L 852646 **292632-98-5**, L 685458
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting presenilin-type aspartic protease signal peptide peptidase with γ-secretase inhibitors in relation to therapeutic uses)

RN 288290-55-1 HCAPLUS

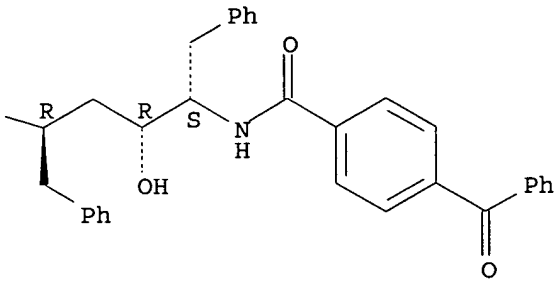
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[(4-benzoylbenzoyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

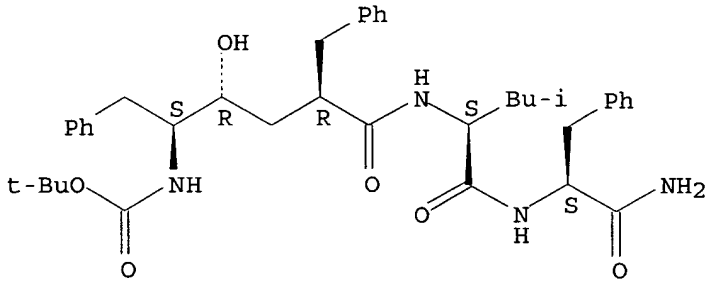


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RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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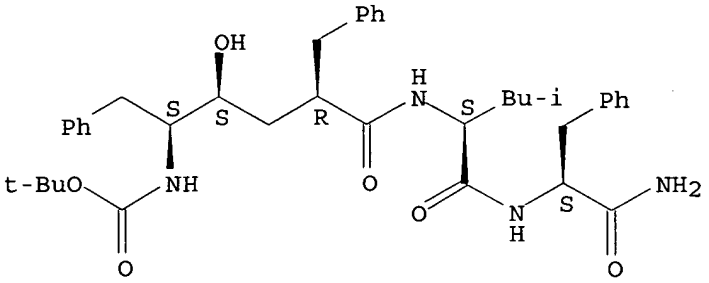
L5 ANSWER 6 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:244253 HCAPLUS
DOCUMENT NUMBER: 139:133817
TITLE: Allyltrichlorostannane additions to α-amino aldehydes: Application to the total synthesis of the aspartyl protease inhibitors L-682,679, L-684,414, L-685,434, and L-685,458
AUTHOR(S): Dias, Luiz C.; Diaz, Gaspar; Ferreira, Andrea A.; Meira, Paulo R. R.; Ferreira, Edilson
CORPORATE SOURCE: Inst. de Quimica, Univ. Estadual de Campinas/UNICAMP, Campinas, 13083-970, Brazil
SOURCE: Synthesis (**2003**), (4), 603-622
CODEN: SYNTBF; ISSN: 0039-7881
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:133817
AB The hydroxyethylene dipeptide isosteres L-682,679, L-684,414, L-685,434, and L-685,458 were synthesized in a few steps by a sequence involving an allyltrichlorostannane coupling with an α-amino aldehyde, followed by hydroboration of the corresponding 1,2-syn and 1,2-anti amino alcs. to give the diols, lactonization under TPAP conditions, lactone opening, and

peptide coupling with the desired amine or dipeptide amide. The present synthetic approach represents a practical entry to a large range of other dipeptide isosteres.

IT **126409-24-3P**, L-682679 **126410-32-0P 338801-69-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereoselective total synthesis of aspartyl protease inhibitors using allyltrichlorostannane addition reaction)

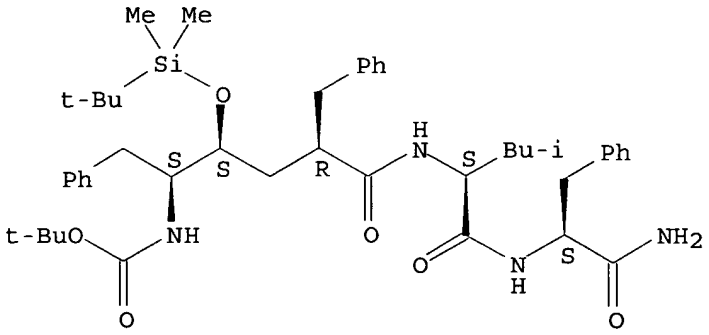
RN 126409-24-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



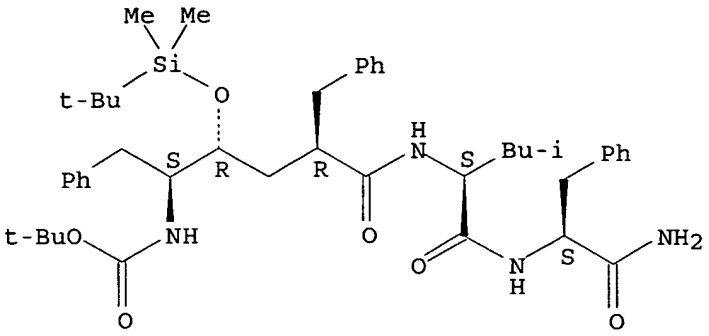
RN 126410-32-0 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



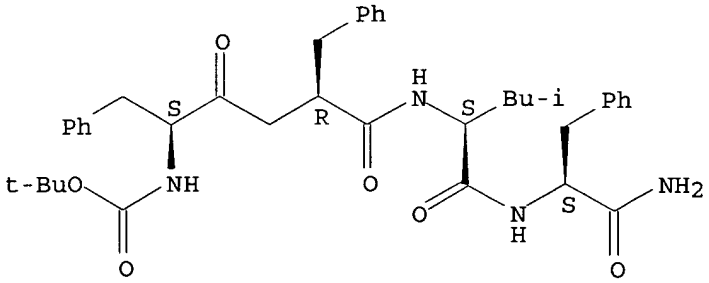
RN 338801-69-7 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



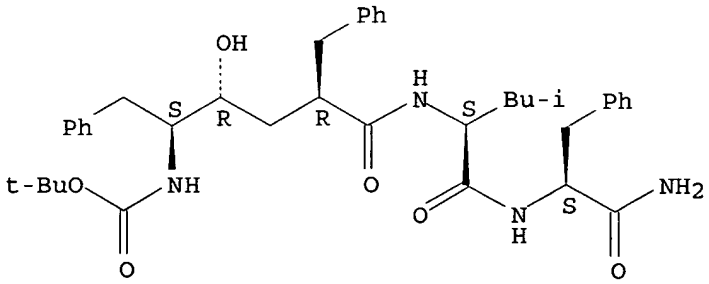
IT **292620-20-3P**, L-684414 **292632-98-5P**, L-685458
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereoselective total synthesis of aspartyl protease inhibitors using allyltrichlorostannane addition reaction)
RN 292620-20-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-1,4-dioxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

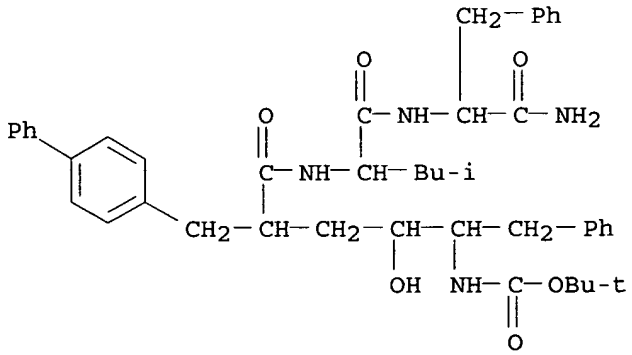
L5 ANSWER 7 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:232517 HCAPLUS
DOCUMENT NUMBER: 138:395422
TITLE: The Signature Molecular Descriptor. 1. Using Extended Valence Sequences in QSAR and QSPR Studies
AUTHOR(S): Faulon, Jean-Loup; Visco, Donald P., Jr.; Pophale, Ramdas S.
CORPORATE SOURCE: Sandia National Laboratories, Livermore, CA, 94551, USA
SOURCE: Journal of Chemical Information and Computer Sciences (2003), 43(3), 707-720
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors present a new descriptor named signature based on extended valence sequence. The signature of an atom is a canonical representation of the atom's environment up to a predefined height h. The signature of a mol. is a vector of occurrence nos. of atomic signatures. Two QSAR and QSPR models based on signature are compared with models obtained using popular mol. 2D descriptors taken from a com. available software (Molconn-Z). One set contains the inhibition concentration at 50% for 121 HIV-1 protease inhibitors, while the second set contains 12865 octanol/water partitioning coeffs. (Log P). For both data sets, the models created by signature performed comparable to those from the com. available descriptors in both correlating the data and in predicting test set values not used in the parametrization. While probing signature's QSAR and QSPR performances, the authors demonstrates that for any given mol. of diameter D, there is a mol. signature of height h ≤ D+1, from which any 2D descriptor can be computed. As a consequence of this finding any QSAR or QSPR involving 2D descriptors can be replaced with a relation involving occurrence number of atomic signatures.

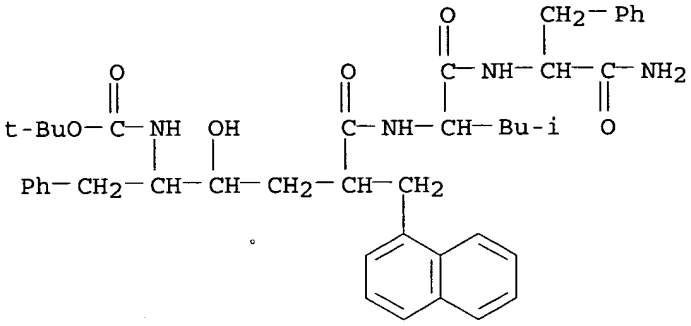
IT **126409-51-6 141221-98-9**
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(HIV-1 protease inhibitor; signature mol. descriptor and using extended valence sequences in QSAR and QSPR studies applied to HIV-1 protease inhibitors and octanol/water partitioning coeffs. and b.ps.)

RN 126409-51-6 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-2-([1,1'-biphenyl]-4-ylmethyl)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenylhexyl]-L-leucyl- (9CI) (CA INDEX NAME)



RN 141221-98-9 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-

4-hydroxy-2-(1-naphthalenylmethyl)-1-oxo-6-phenylhexyl]-L-leucyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:173459 HCAPLUS
DOCUMENT NUMBER: 138:217451
TITLE: Preparation, substrate specificity, and therapeutic uses of human γ3 protease involved in processing of amyloid precursor protein
INVENTOR(S): Crouthamel, Ming-Chih; Gardell, Stephen J.; Huang, Qian; Lai, Ming-Tain; Li, Yueming
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003018050	A1	20030306	WO 2002-US26969	20020808 <--
W: CA, JP, US				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR				
EP 1427439	A1	20040616	EP 2002-768689	20020808
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: US 2001-311410P P 20010810
WO 2002-US26969 W 20020808

AB The invention provides γ3 protease, a novel aspartyl class protease that is capable of taking part in the processing of amyloid precursor protein (APP) to Aβ peptide. The γ3 protease may be involved in the development and/or progression of Alzheimer's disease. It has a Mr of 60-120 kDa on gel filtration, and its activity is inhibited by pepstatin A but not by L685,458 (a known γ-secretase inhibitor) with a pH optimum of 6.0. γ3 Protease cleaves amyloid precursor protein, as well as artificial substrates incorporating portions of APP695, at the same or similar sites as γ-secretase, but can be distinguished from the known γ-secretase activity involving presenilin-1 and presenilin-2. Methods of assaying γ3 protease and identifying potential inhibitors, useful in the prevention or treatment of Alzheimer s

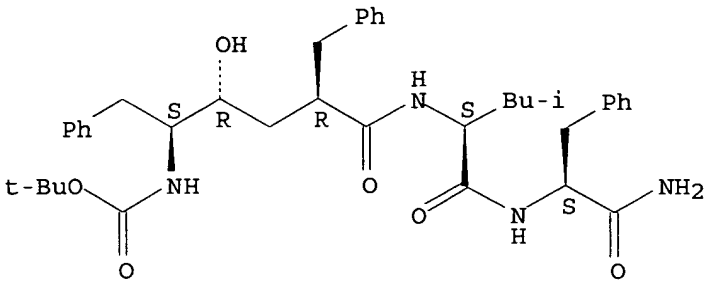
disease, are disclosed.

IT **292632-98-5**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(lack of γ3 protease inhibition by and purification in presence of; preparation, substrate specificity, and therapeutic uses of human γ3 protease involved in processing of amyloid precursor protein)

RN 292632-98-5 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:112268 HCAPLUS
DOCUMENT NUMBER: 139:65197
TITLE: Selecting cells with different Alzheimer's disease γ-secretase activity using FACS. Differential effect of presenilin exon 9 deletion on γ- and ε-cleavage
AUTHOR(S): Sernee, M. Fleur; Evin, Genevieve; Culvenor, Janetta G.; Villadangos, Jose A.; Beyreuther, Konrad; Masters, Colin L.; Cappai, Roberto
CORPORATE SOURCE: Department of Pathology, The University of Melbourne and The Mental Health Research Institute, Parkville, Australia
SOURCE: European Journal of Biochemistry (2003), 270(3), 495-506
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ultimate step in Alzheimer's disease Aβ generation involves γ-secretase, which releases Aβ from its membrane-bound precursor. A similar presenilin-dependent proteolytic activity is implicated in the release of the Notch intracellular domain. The authors have developed a novel assay for γ-secretase activity based on green fluorescent protein detection. This involves cotransfection of a substrate-activator based on the amyloid precursor protein or the Notch sequence and a fluorescent reporter gene. Stable fluorescent cell populations were selected by fluorescent activated cell sorting and characterized. This assay enabled the identification and sorting of populations, which differ in their levels of γ-secretase activity, with high fluorescent cells producing more Aβ than low fluorescent

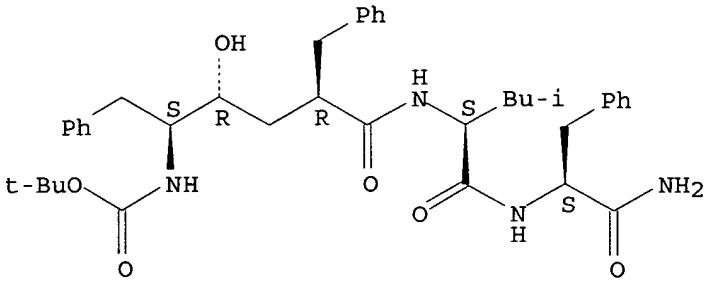
cells. Specific γ-secretase inhibitors, L-685,458 and MW167, reduced cell fluorescence in a dose-dependent manner that paralleled inhibition of Aβ secretion. Overexpression of presenilin 1 increased the cell fluorescence. Cells expressing presenilin with different aspartate mutations (D257A, D385A and D257A/D385A) or exon 9 deletion mutation showed reduced fluorescence. The single aspartate mutations showed a concomitant reduction in Aβ secretion, whereas the D257A/D385A and ΔE9 mutations had no effect on Aβ secretion.

IT **292632-98-5**, L-685458
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(inhibitor; γ-secretase inhibitors effect on GFP protein fluorescence in assay for Alzheimer's disease γ-secretase)

RN 292632-98-5 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



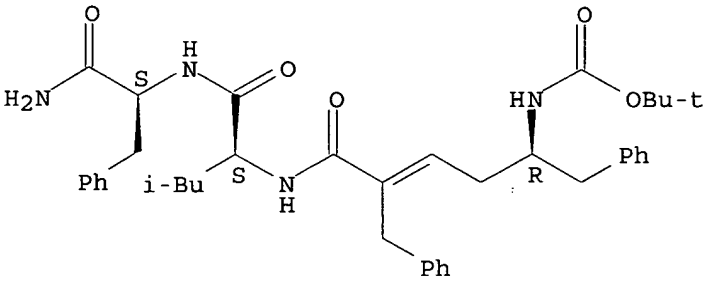
REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:925001 HCAPLUS
DOCUMENT NUMBER: 139:46900
TITLE: Synthesis and γ-secretase activity of APP substrate-based hydroxyethylene dipeptide isosteres
AUTHOR(S): Nadin, Alan; Owens, Andrew P.; Castro, Jose L.; Harrison, Timothy; Shearman, Mark S.
CORPORATE SOURCE: Merck Sharp & Dohme Research Laboratories, Department of Medicinal Chemistry, The Neuroscience Research Centre, Harlow, Essex, CM20 2QR, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2003**), 13(1), 37-41
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two new APP substrate-based hydroxyethylene isosteres (AT and VI) were prepared and their dipeptide conjugates shown not to inhibit the γ-secretase-mediated formation of either Aβ1-40 or Aβ1-42. The FG isostere and a des-hydroxy hydroxyethylene isostere also gave inactive compds. Conversely, a number of compds. containing the intact substrate-unrelated Phe-Phe (FF) hydroxyethylene isostere were shown to be potent inhibitors (ED50=14-732 nM). These results show that the factors governing the substrate-based design of γ-secretase inhibitors are more complicated than first thought.

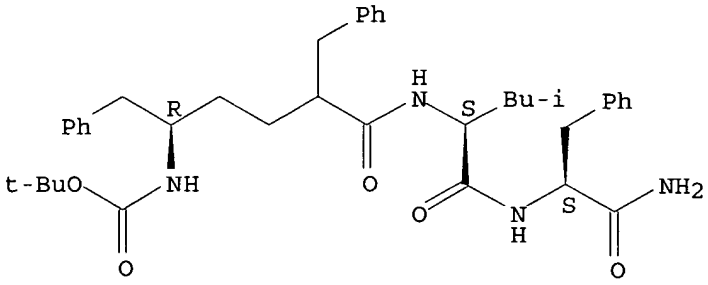
IT **545375-24-4P 545375-25-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and γ-secretase activity of APP substrate-based hydroxyethylene dipeptide isosteres)
RN 545375-24-4 HCAPLUS
CN L-Phenylalaninamide, N-[(5R)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxo-6-phenyl-2-(phenylmethyl)-2-hexenyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



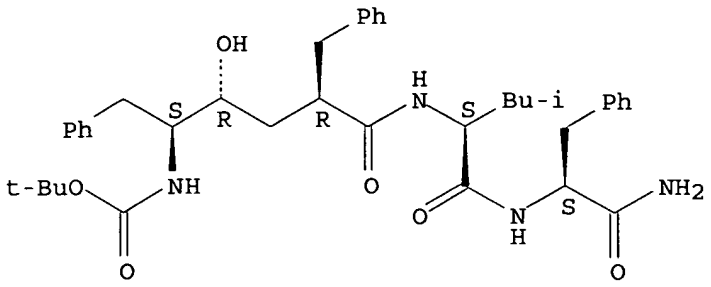
RN 545375-25-5 HCAPLUS
CN L-Phenylalaninamide, N-[(5R)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **292632-98-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and γ-secretase activity of APP substrate-based hydroxyethylene dipeptide isosteres)
RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

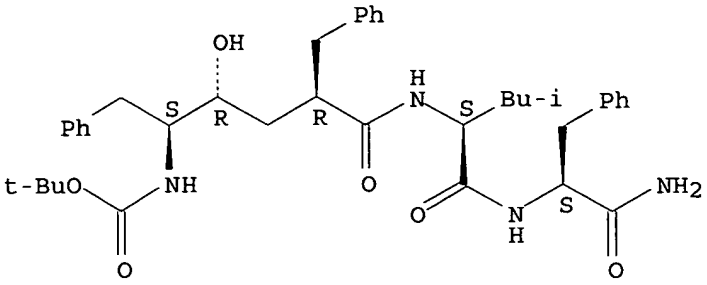
L5 ANSWER 11 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:913850 HCAPLUS
DOCUMENT NUMBER: 138:301929
TITLE: γ-Secretase: characterization and implication for Alzheimer disease therapy
AUTHOR(S): Xu, Min; Lai, Ming-Tain; Huang, Qian; DiMuzio-Mower, Jillian; Castro, Jose L.; Harrison, Timothy; Nadin, Alan; Neduvelil, Joseph G.; Shearman, Mark S.; Shafer, Jules A.; Gardell, Stephen J.; Li, Yue-Ming
CORPORATE SOURCE: Department of Biological Chemistry, WP16-206, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Neurobiology of Aging (**2002**), 23(6), 1023-1030
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB γ-Secretase is a membrane-bound protease that cleaves within the transmembrane region of amyloid precursor protein to generate the C-termini of the Aβ peptides which are believed to play a central role in the neuropathol. of Alzheimer's disease. An in vitro γ-secretase assay using a recombinant substrate C100Flag was developed to facilitate the characterization and identification of this enigmatic protease. Biochem. studies establish that γ-secretase activity is catalyzed by a PS1-containing macromol. complex. Moreover, the fact that the photoreactive active γ-secretase inhibitor directed to the active site labels PS1 suggests that PS1 contains the active site of the protease. Presenilin/γ-secretase as a potential target for AD therapy and its role in regulated intramembrane proteolysis are discussed.

IT **292632-98-5**, L-685458 **507453-70-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PS1-containing γ-secretase complex, characterization and photoreactive, active site-directed inhibitors in Alzheimer disease therapy)

RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

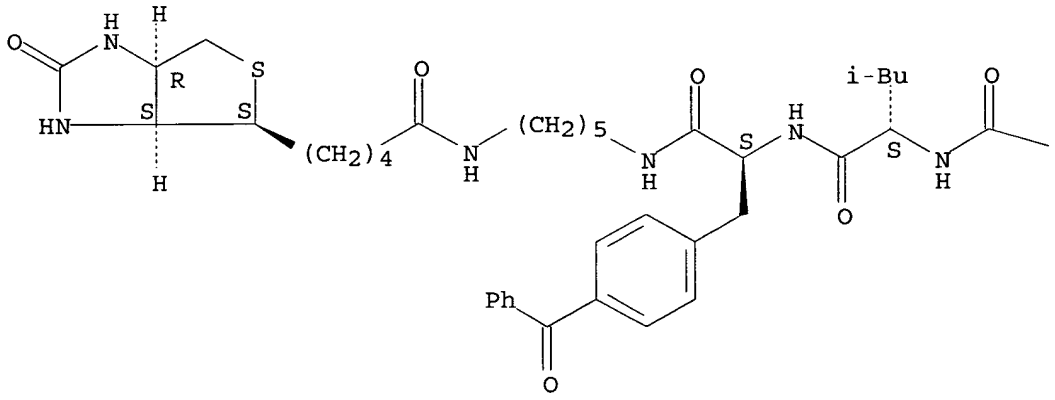
Absolute stereochemistry. Rotation (-).



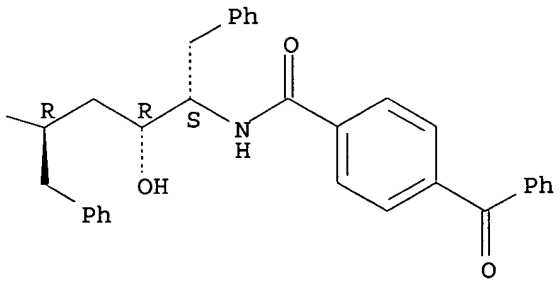
RN 507453-70-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[(4-benzoylbenzoyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-4-benzoyl-N-[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searched by P. Ruppel

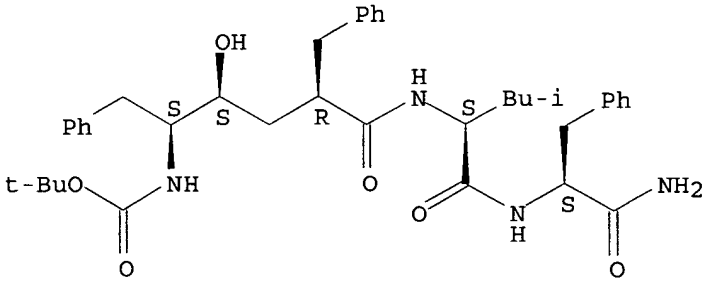
L5 ANSWER 12 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:859451 HCAPLUS
DOCUMENT NUMBER: 138:188058
TITLE: Short total synthesis of aspartyl protease inhibitors L-685,434, L-682,679 and L-685,458
AUTHOR(S): Dias, Luiz C.; Ferreira, Andrea A.; Diaz, Gaspar
CORPORATE SOURCE: Instituto de Quimica, Universidade Estadual de Campinas/UNICAMP, Campinas, CEP: 13083-970, Brazil
SOURCE: Synlett (**2002**), (11), 1845-1849
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:188058

AB Hydroxyethylene dipeptide isosteres L-685,434, L-682,679 and L-685,458 were synthesized in a few steps by a sequence involving an allyltrichlorostannane coupling with an α-aminoaldehyde followed by hydroboration of the corresponding 1,2-syn and 1,2-anti amino alcs. to give the diols, lactonization under TPAP conditions, lactone opening and peptide coupling with the desired amine or dipeptide amide.

IT **126409-24-3P**, L682679
RL: SPN (Synthetic preparation); PREP (Preparation)
(total synthesis of L682679 as HIV-1 protease inhibitor by coupling of allyltrichlorostannane with aminoaldehyde, hydroboration, lactonization, lactone opening and peptide coupling)

RN 126409-24-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

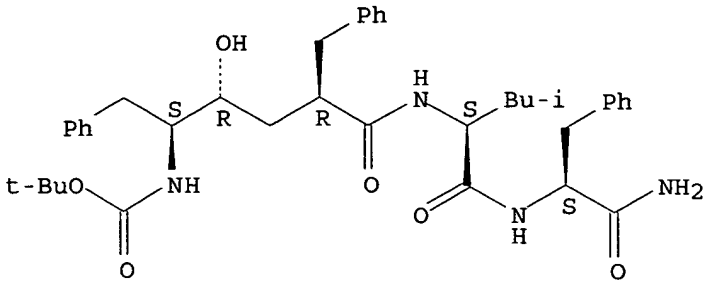
Absolute stereochemistry.



IT **292632-98-5P**, L685458
RL: SPN (Synthetic preparation); PREP (Preparation)
(total synthesis of L685458 as γ-secretase inhibitor by coupling of allyltrichlorostannane with aminoaldehyde, hydroboration, lactonization, lactone opening and peptide coupling)

RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

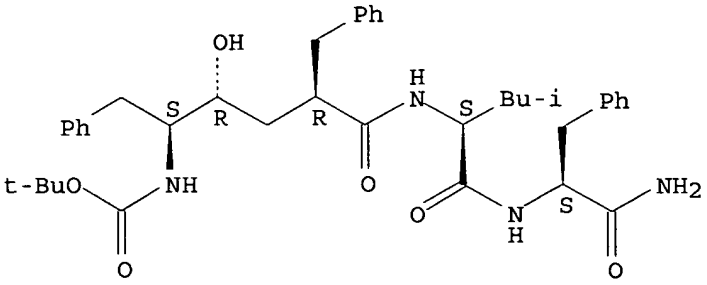
L5 ANSWER 13 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:677933 HCAPLUS
DOCUMENT NUMBER: 138:283161
TITLE: Linear non-competitive inhibition of solubilized human γ-secretase by pepstatin A methylester, L685458, sulfonamides, and benzodiazepines
AUTHOR(S): Tian, Gaochao; Sobotka-Briner, Cynthia D.; Zysk, John; Liu, Xiaodong; Birr, Cynthia; Sylvester, Mark A.; Edwards, Philip D.; Scott, Clay D.; Greenberg, Barry D.
CORPORATE SOURCE: Department of Lead Discovery, AstraZeneca Pharmaceuticals, Wilmington, DE, 19850, USA
SOURCE: Journal of Biological Chemistry (**2002**), 277(35), 31499-31505
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cerebral deposition of amyloid β-protein (Aβ) is believed to play a key role in the pathogenesis of Alzheimer's disease. Because Aβ is produced from the processing of amyloid β-protein precursor (APP) by β- and γ-secretases, these enzymes are considered important therapeutic targets for identification of drugs to treat Alzheimer's disease. Unlike β-secretase, which is a monomeric aspartyl protease, γ-secretase activity resides as part of a membrane-bound, high mol. weight, macromol. complex. Pepstatin and L685458 are among several structural classes of γ-secretase inhibitors identified so far. These compds. possess a hydroxyethylene dipeptide isostere of aspartyl protease transition state analogs, suggesting γ-secretase may be an aspartyl protease. However, the mechanism of inhibition of γ-secretase by pepstatin and L685458 has not been elucidated. In this study, we report that pepstatin A methylester and L685458 unexpectedly displayed linear non-competitive inhibition of γ-secretase. Sulfonamides and benzodiazepines, which do not resemble transition state analogs of aspartyl proteases, also displayed potent, non-competitive inhibition of γ-secretase. Models to rationalize how transition state analogs inhibit their targets by non-competitive inhibition are discussed.

IT **292632-98-5**, L685458
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(linear non-competitive inhibition of solubilized human γ-secretase by pepstatin A methylester, L685458, sulfonamides, and benzodiazepines)

RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:90606 HCAPLUS
DOCUMENT NUMBER: 136:135035
TITLE: Preparation of peptidomimetics for use as γ-secretase inhibitors in the study of amyloid protein precursor processing
INVENTOR(S): Nadin, Alan John; Neduvelil, Joseph George; Sardana, Mohinder K.; Shafer, Jules A.; Gardell, Stephen J.; Lai, Ming-Tain; Li, Yueming; Dorsey, Bruce D.; Dean, Dennis C.
PATENT ASSIGNEE(S): Merck & Co., Inc., UK
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
US 2002013276	A1	20020131	US 2001-797820		20010302	<--
US 6753410	B2	20040622				
PRIORITY APPLN. INFO.:			US 2000-186578P	P	20000302	

OTHER SOURCE(S): MARPAT 136:135035
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. [e.g., (I)], for use as photoaffinity labels and enzyme inhibitors of γ-secretase in the investigation of amyloidosis in the development of Alzheimer's disease, were prepared Starting from tert-Bu [1S-(5-oxo-tetrahydrofuran-2R-yl)2-phenylethyl]-carbamate, the lactone ring was benzylated and then ring-opened, the free hydroxy group protected with the tert-butyldimethylsilyl group, and the product reacted with 4-benzoylphenylalanine and then Boc-Leu-OH. Further chain extension

steps, culminating in reaction with sulfosuccinimidyl-2-(biotinamide)ethyl-1,3-dithiopropionate, gave I. Title compds. were discussed as having an activity as inhibitors of γ-secretase, and to inhibit proteolysis of presenilin-1 (no data).

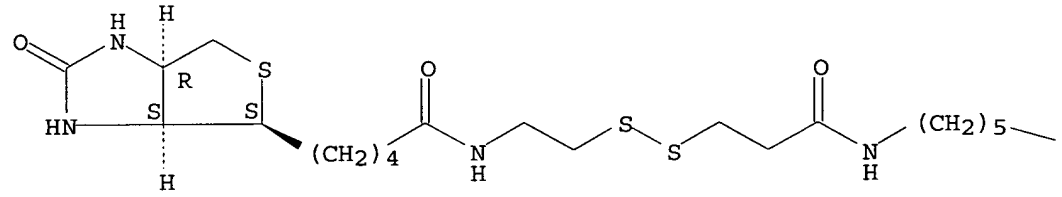
IT **392658-40-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of peptidomimetics for use as γ-secretase inhibitors in the study of amyloid protein precursor processing)

RN 392658-40-1 HCAPLUS

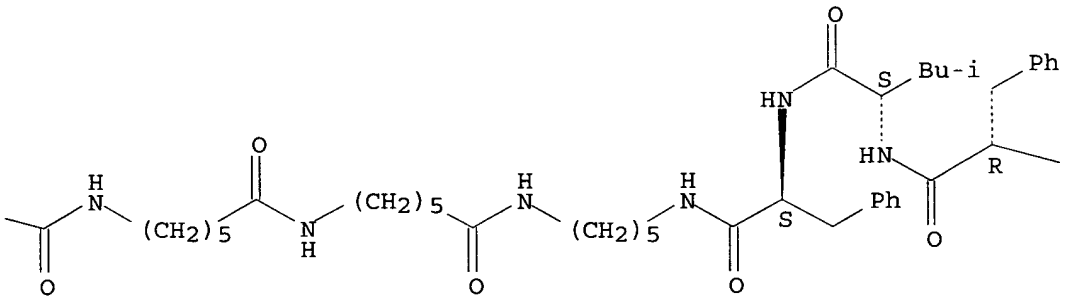
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[40-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-7,14,21,28,36-pentaoxo-31,32-dithia-6,13,20,27,35-pentaazatetracont-1-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

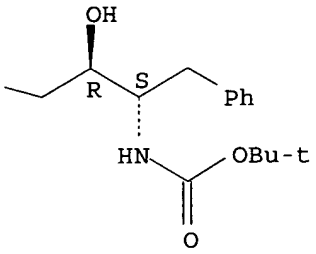
PAGE 1-A



PAGE 1-B



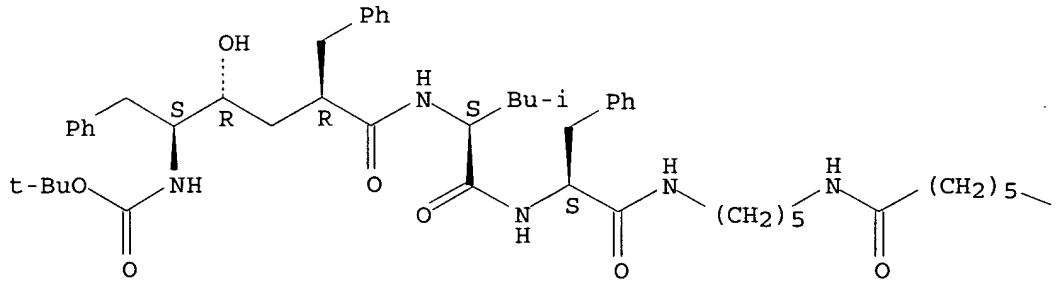
PAGE 1-C



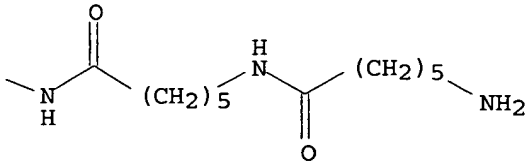
IT **392658-39-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptidomimetics for use as γ-secretase inhibitors in the study of amyloid protein precursor processing)
RN 392658-39-8 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[6-[[6-[(6-amino-1-oxohexyl)amino]-1-oxohexyl]amino]-1-oxohexyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

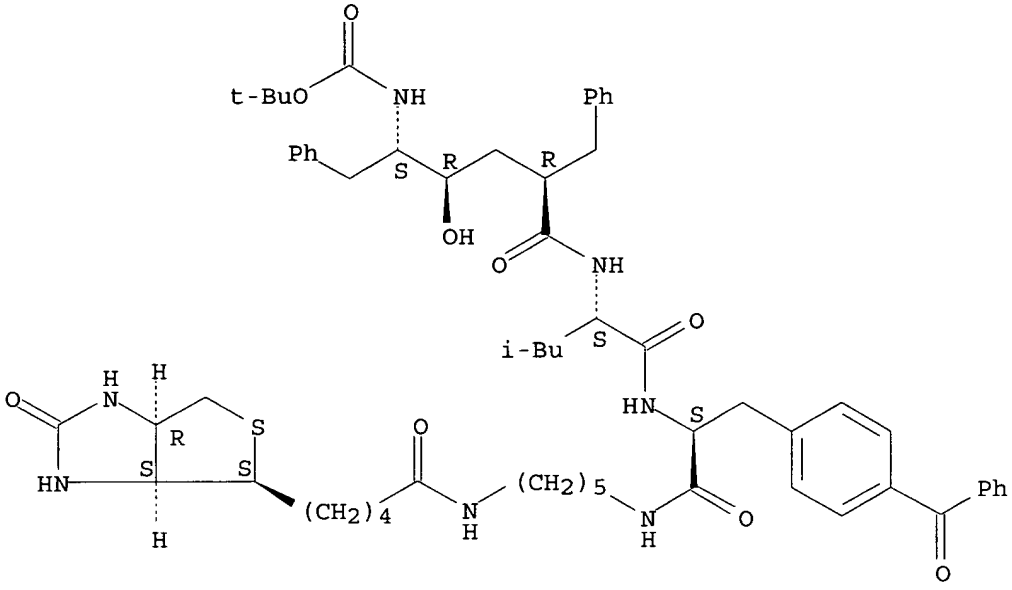


IT **288290-54-0P 288290-55-1P 392690-03-8P**
392690-05-0P 392690-07-2P 392690-09-4P
392690-11-8P 392690-13-0P 392690-16-3P

392690-18-5P 392690-20-9P 392690-24-3P
392690-26-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of peptidomimetics for use as γ-secretase inhibitors in the study of amyloid protein precursor processing)

RN 288290-54-0 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-4-benzoyl-N-[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]- (9CI) (CA INDEX NAME)

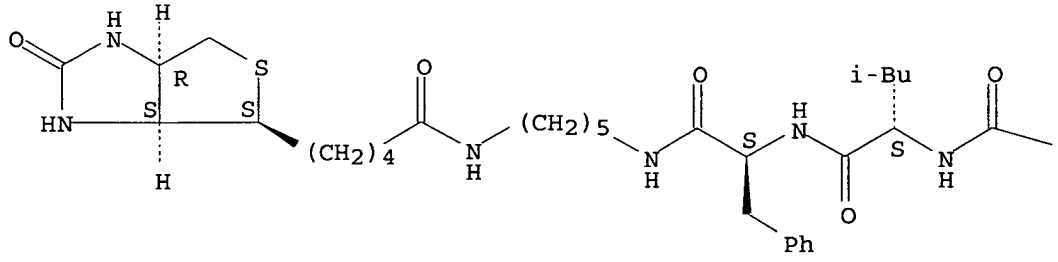
Absolute stereochemistry.



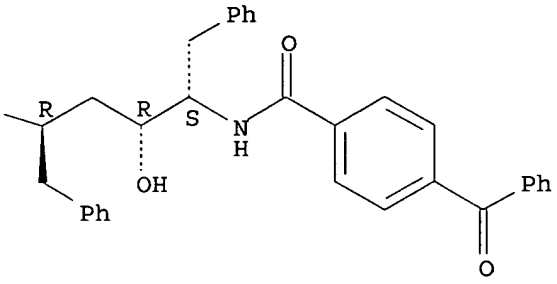
RN 288290-55-1 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[(4-benzoylbenzoyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

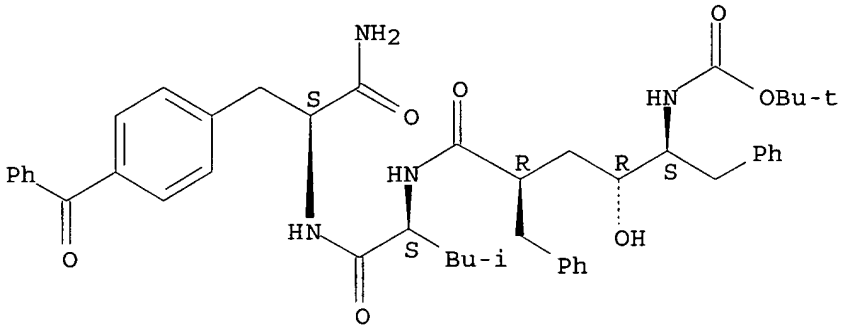


PAGE 1-B



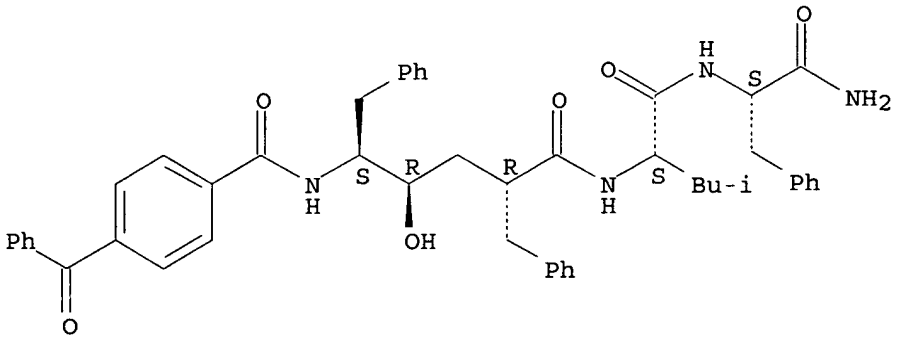
RN 392690-03-8 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-4-benzoyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 392690-05-0 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[(4-benzoylbenzoyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

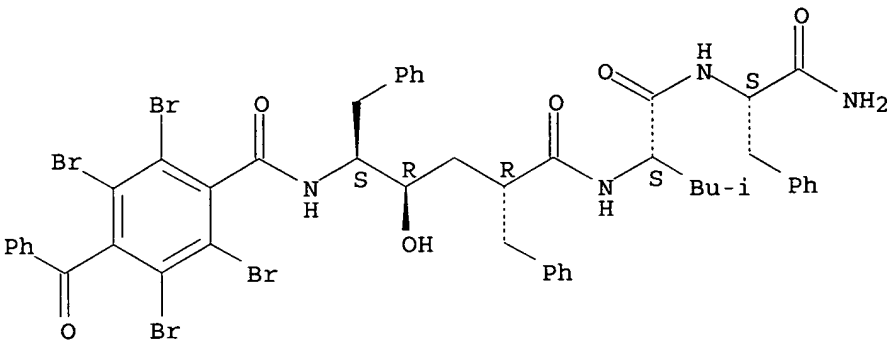
Absolute stereochemistry.



RN 392690-07-2 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[(4-benzoyl-2,3,5,6-tetrabromobenzoyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-

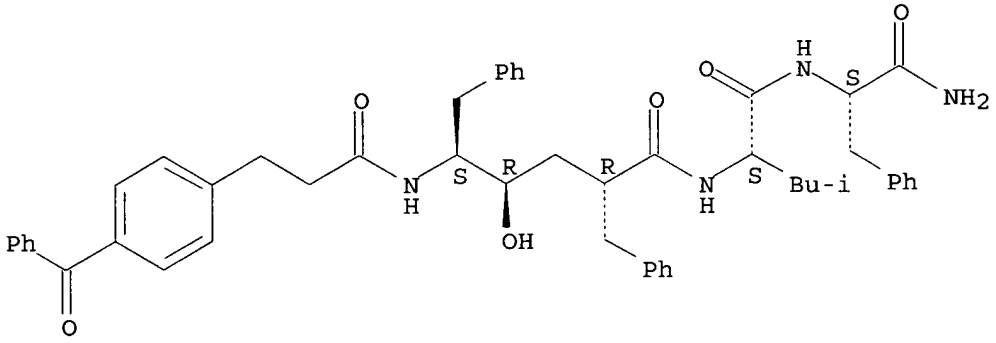
leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



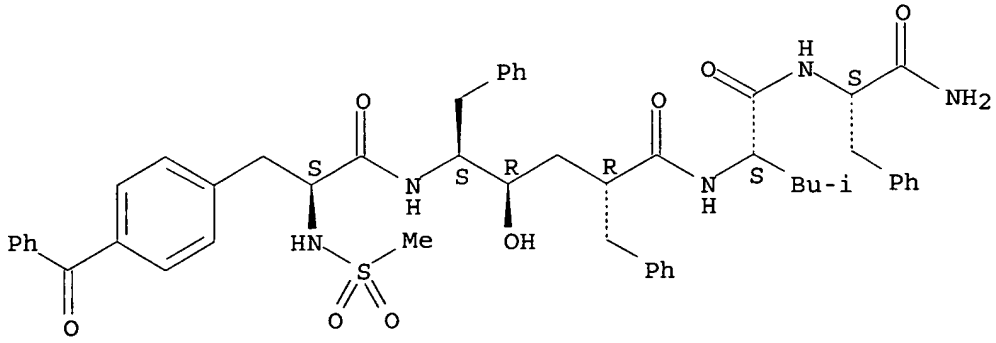
RN 392690-09-4 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[3-(4-benzoylphenyl)-1-oxopropyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



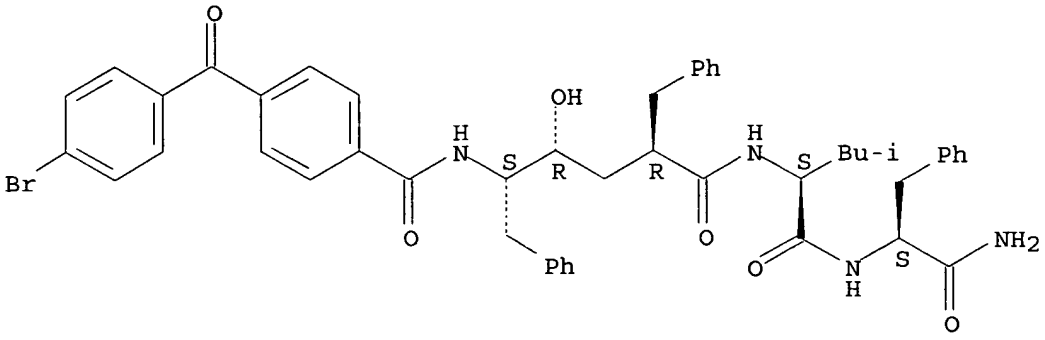
RN 392690-11-8 HCAPLUS
CN L-Phenylalaninamide, 4-benzoyl-N-(methylsulfonyl)-L-phenylalanyl-(αR,γR,δS)-δ-amino-γ-hydroxy-α-(phenylmethyl)benzenehexanoyl-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 392690-13-0 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[4-(4-bromobenzoyl)benzoyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

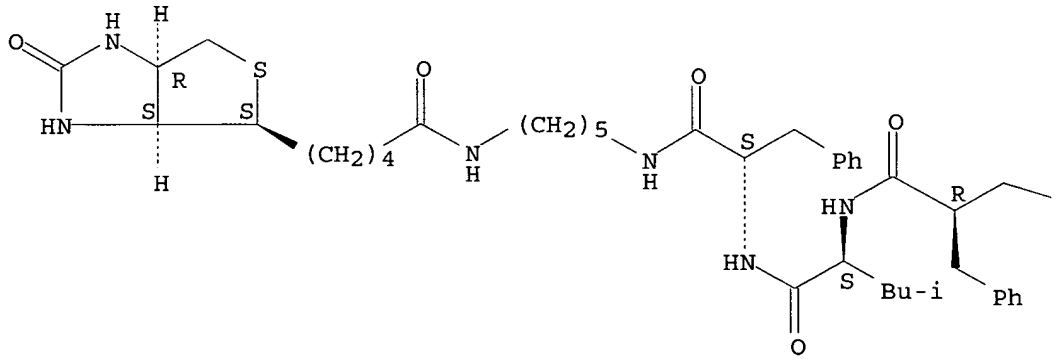
Absolute stereochemistry.



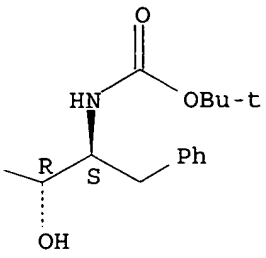
RN 392690-16-3 HCAPLUS
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Absolute stereochemistry.

PAGE 1-A



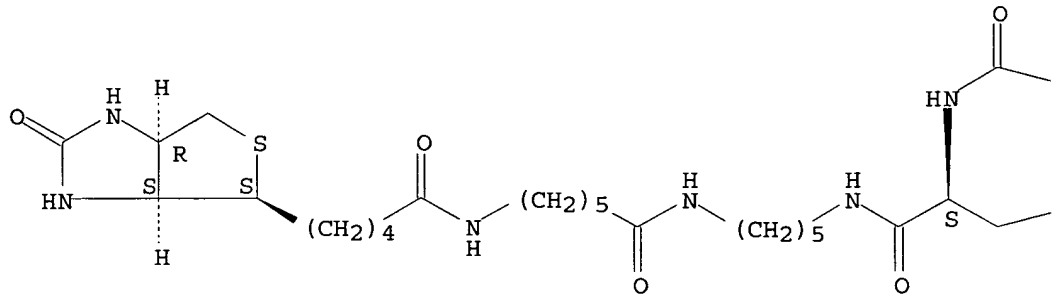
PAGE 1-B



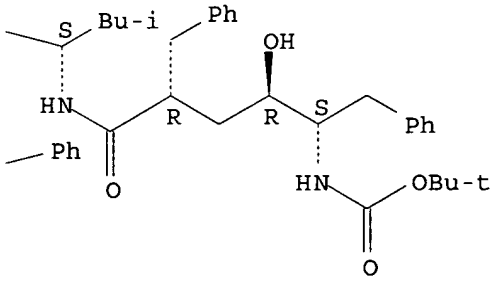
RN 392690-18-5 HCAPLUS
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Absolute stereochemistry.

PAGE 1-A



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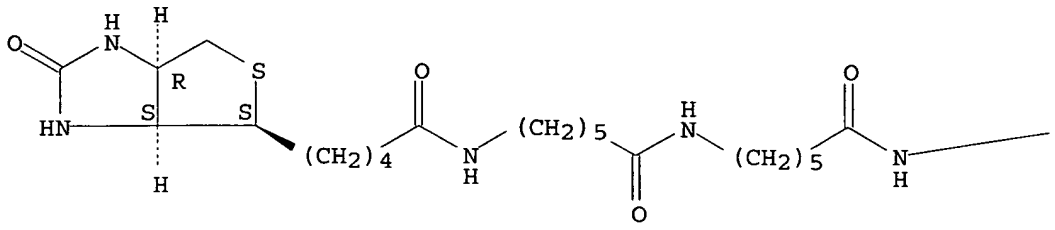


RN 392690-20-9 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[6-[[6-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]-1-oxohexyl]amino]-1-oxohexyl]amino]pentyl]- (9CI) (CA

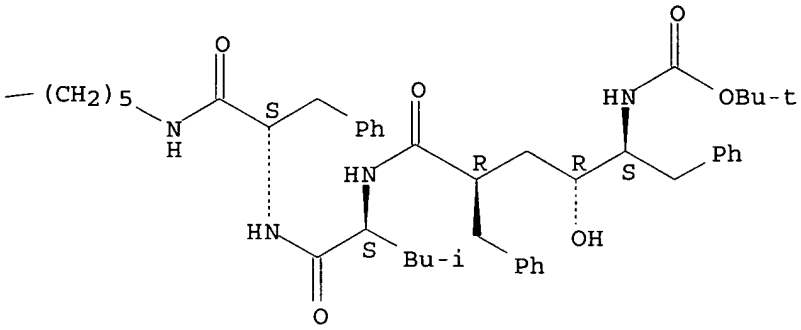
INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



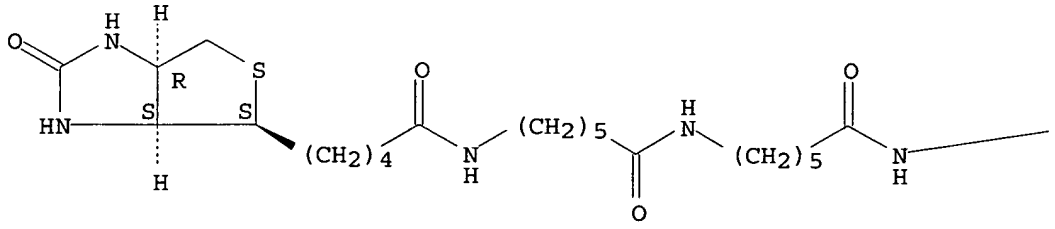
PAGE 1-B



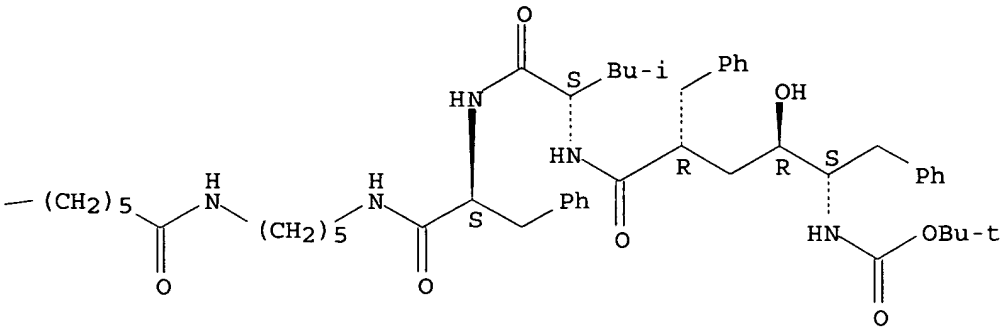
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Absolute stereochemistry.

PAGE 1-A



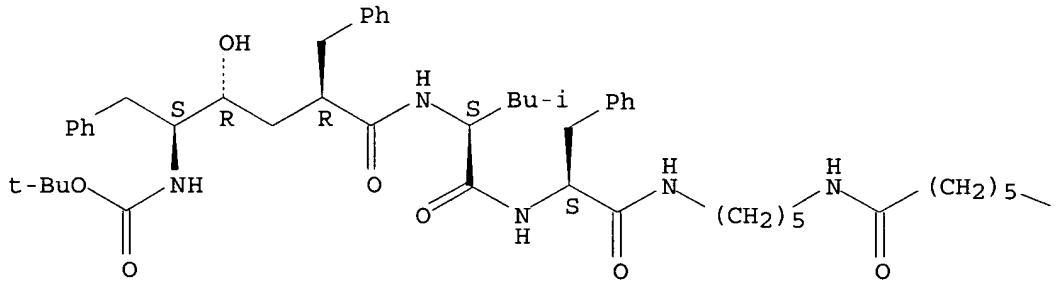
PAGE 1-B



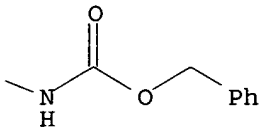
RN 392690-26-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[1-oxo-6-[[(phenylmethoxy)carbonyl]amino]hexyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:893450 HCAPLUS
DOCUMENT NUMBER: 136:177478
TITLE: Pharmacological knock-down of the presenilin 1 heterodimer by a novel γ-secretase inhibitor.

Implications for presenilin biology

AUTHOR(S): Beher, Dirk; Wrigley, Jonathan D. J.; Nadin, Alan; Evin, Genevieve; Masters, Colin L.; Harrison, Timothy; Castro, Jose L.; Shearman, Mark S.

CORPORATE SOURCE: Departments of Biochemistry & Molecular Biology, Merck Sharp & Dohme Research Laboratories, The Neuroscience Research Centre, Essex, CM20 2QR, UK

SOURCE: Journal of Biological Chemistry (**2001**), 276(48), 45394-45402
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 136:177478

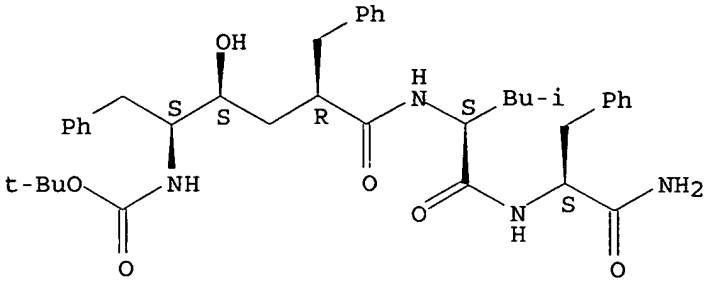
AB Intramembranous cleavage of the β-amyloid precursor protein by γ-secretase is the final processing event generating amyloid-β peptides, which are thought to be causative agents for Alzheimer's disease. Missense mutations in the presenilin genes co-segregate with early-onset Alzheimer's disease, and, recently, a close biochem. linkage between presenilins and the identity of γ-secretase has been established. Here we describe for the first time that certain potent γ-secretase inhibitors are able to interfere with the endoproteolytic processing of presenilin 1 (PS1). In addition, we identified a novel γ-secretase inhibitor, [S-benzyl-4R-[1-(5-cyclohexyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3(R,S)-ylcarbamoyl)-S-ethylcarbamoyl]-2R-hydroxy-5-phenyl-pentyl]-carbamic acid tert-Bu ester (CBAP), which not only phys. interacts with PS1, but upon chronic treatment produces a "pharmacol. knock-down" of PS1 fragments. This indicates that the observed accumulation of full-length PS1 is caused by a direct inhibition of its endoproteolysis. The subsequent use of CBAP as a biol. tool to increase full-length PS1 levels in the absence of exogenous PS1 expression has provided evidence that wild-type PS1 endoproteolysis is not required either for PS1/γ-secretase complex assembly or trafficking. Furthermore, in cell-based systems CBAP does not completely recapitulate PS1 loss-of-function phenotypes. Even though the β-amyloid precursor protein cleavage and the S3 cleavage of the Notch receptor are inhibited by CBAP, an impairment of Trk receptor maturation was not observed

IT **126409-24-3**, L-682679 **292632-98-5**, L-685458 **392690-26-5**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (pharmacol. knock-down of presenilin 1 heterodimer by γ-secretase inhibitor)

RN 126409-24-3 HCAPLUS

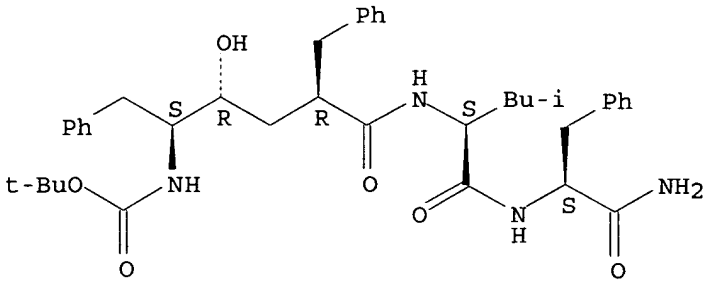
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

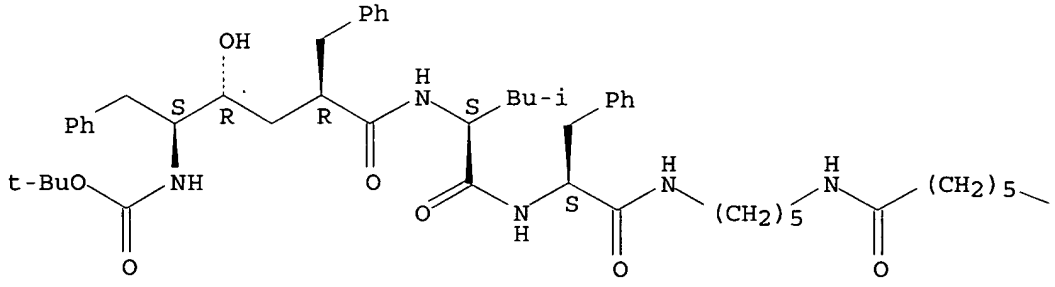
Absolute stereochemistry. Rotation (-).



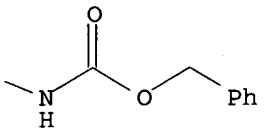
RN 392690-26-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[1-oxo-6-[[(phenylmethoxy)carbonyl]amino]hexyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:763032 HCAPLUS
DOCUMENT NUMBER: 135:304145
TITLE: Preparation of peptides as γ-secretase inhibitors
INVENTOR(S): Nadin, Alan John; Stevenson, Graeme Irvine
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077144	A1	20011018	WO 2001-GB1549	20010404 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003100512	A1	20030529	US 2002-257058	20021007 <--
PRIORITY APPLN. INFO.:			GB 2000-8710 A	20000407
			WO 2001-GB1549 W	20010404

OTHER SOURCE(S): MARPAT 135:304145

AB Peptides R1-X-CONR2CH2-B-CH2CHR3CONHCHR4CON(A)[CHR5CON(A)]n-A [R1 = (un)substituted alkyl, alkenyl, alkynyl, Ph, naphthyl or heterocyclyl; R2, R3 = any group given for R1 or (un)substituted alkoxy, alkenyloxy or alkynyloxy; R4, R5 = H, (un)substituted alkyl; A = H, (un)substituted alkyl, alkenyl, alkynyl or heterocyclyl; B = CO or CHOH in the R configuration; X = O or a bond; n = 0 or 1] were prepared as γ-secretase inhibitors which find use in the treatment and/or prevention of Alzheimer's disease. Thus, (R,R)-Boc-N(CH2CH2Ph)CH2CH(OH)CH2CH(CH2Ph)CO-Leu-Phe-NH2 (Boc = tert-butoxycarbonyl) was prepared from 4S-benzyl-3-(2R-oxiranyl-3-phenylpropionyl)oxazolidin-2-one by phenethylamination/protection with Boc2O to afford (4R-benzyl-5-oxotetrahydrofuran-2(RS)-ylmethyl)phenethylcarbamic acid tert-Bu ester, which underwent sequential ring cleavage with LiOH/dioxane,

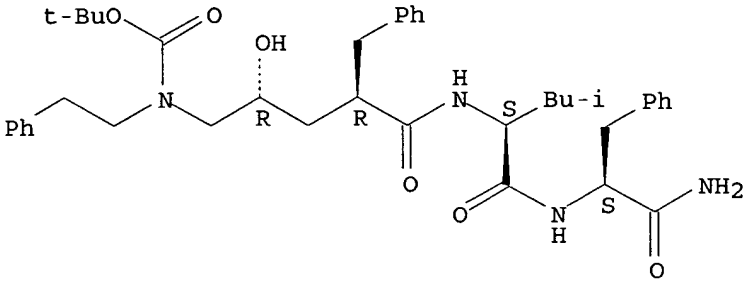
silyl protection with TBSCl, coupling with H-Leu-Phe-NH2, deprotection, treatment with PCC/NaBH4, and separation of the diastereomer by HPLC.

IT **366797-75-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides as γ-secretase inhibitors)

RN 366797-75-3 HCAPLUS

CN L-Phenylalaninamide, N-[2,3,5-trideoxy-5-[[(1,1-dimethylethoxy)carbonyl](2-phenylethyl)amino]-2-(phenylmethyl)-L-threo-pentonoyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

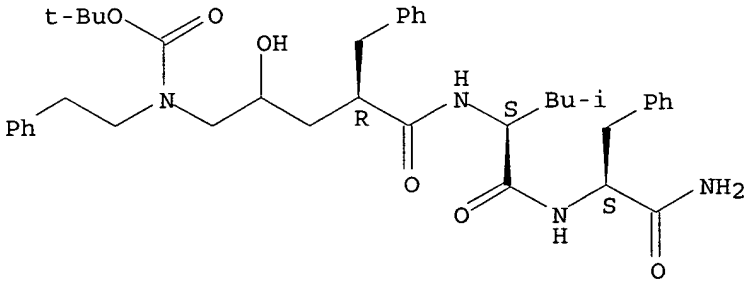


IT **366797-83-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptides as γ-secretase inhibitors)

RN 366797-83-3 HCAPLUS

CN L-Phenylalaninamide, N-[(4ξ)-2,3,5-trideoxy-5-[[(1,1-dimethylethoxy)carbonyl](2-phenylethyl)amino]-2-(phenylmethyl)-D-glycero-pentonoyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

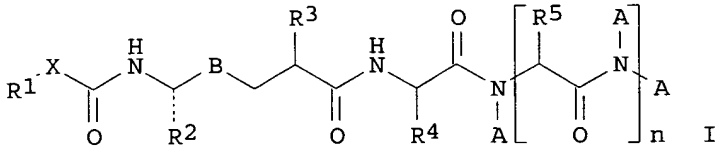
L5 ANSWER 17 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:545658 HCAPLUS
DOCUMENT NUMBER: 135:122753
TITLE: Preparation of peptide derivatives as γ-secretase inhibitors
INVENTOR(S): Castro Pineiro, Jose Luis; Harrison, Timothy; Hunt, Peter Alan; Nadin, Alan John
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK

SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001053255	A1	20010726	WO 2001-GB200	20010119 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2397543	AA	20010726	CA 2001-2397543	20010119 <--
AU 2001026933	A5	20010731	AU 2001-26933	20010119 <--
EP 1254108	A1	20021106	EP 2001-901274	20010119 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003520266	T2	20030702	JP 2001-553260	20010119 <--
US 2003114387	A1	20030619	US 2002-181871	20020718 <--
US 6756511	B2	20040629		

PRIORITY APPLN. INFO.:
GB 2000-1589 A 20000124
GB 2000-3767 A 20000217
WO 2001-GB200 W 20010119

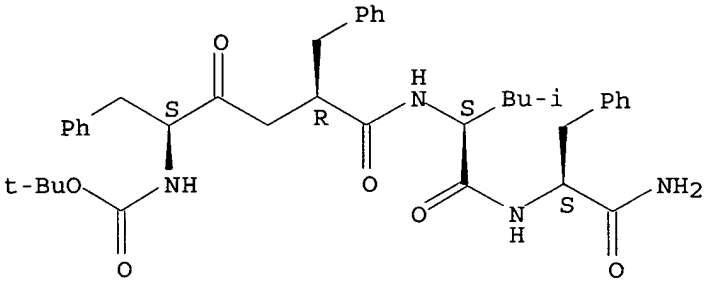
OTHER SOURCE(S): MARPAT 135:122753
GI



AB Compds. I [R1 = (un)substituted C1-10-alkyl, C2-10-alkenyl or -alkynyl, Ph, naphthyl, a five-membered heterocyclic ring containing 1-4 heteroatoms (O, N or S, at most one of the heteroatoms being O or S), a six-membered heterocyclic ring containing 1-3 N atoms; R2, R3 = (un)substituted C1-10-alkyl or -alkoxy, C2-10-alkenyl, -alkenyloxy, -alkynyl, or -alkynyloxy, Ph, naphthyl, a five- or six-membered heteroarom. ring, (CH2)0-3Q1, where Q1 is five- or six-membered heterocyclyl; alternatively, R3 may be H; R4, R5 = H, C1-6 optionally substituted by halogen, hydroxy, thiol, amino, C1-4-alkoxy, -alkylthio, or -alkoxycarbonyl, carboxy, (CH2)0-3Q2, where Q2 is a five- or six-membered unsatd. heterocycle; A = H, (un)substituted C1-10-alkyl, C2-10-alkenyl or -alkynyl, a seven-membered heterocycle; B = CO or CHOH in the R-configuration; X = O or a bond; n = 0 or 1] were prepared as γ-secretase inhibitors for use in the treatment or prevention of Alzheimer's disease. Thus, [1(S)-benzyl-4(R)-[1(S)-[1(S)-carbamoyl-2(R)-hydroxypropylcarbamoyl]ethylcarbamoyl]-2(R)-hydroxy-5-phenylpentyl]carbamic acid tert-Bu ester was prepared by treating [1S-(5-oxotetrahydrofuran-2R-yl)-2-phenylethyl]carbamic acid tert-Bu ester sequentially with BzH, tert-BuSiMe2Cl, and H-L-Ala-L-Thr-NH2.

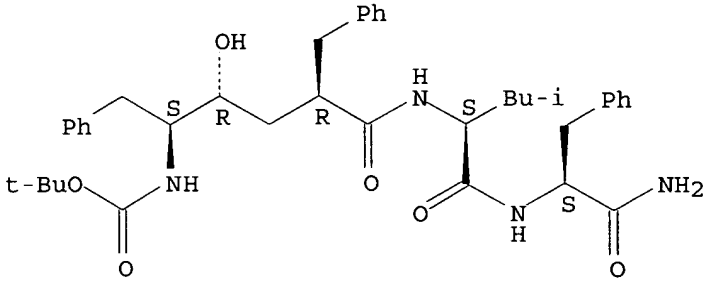
IT **292620-20-3P 292632-98-5P 350981-88-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide derivs. as γ-secretase inhibitors)
RN 292620-20-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-1,4-dioxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



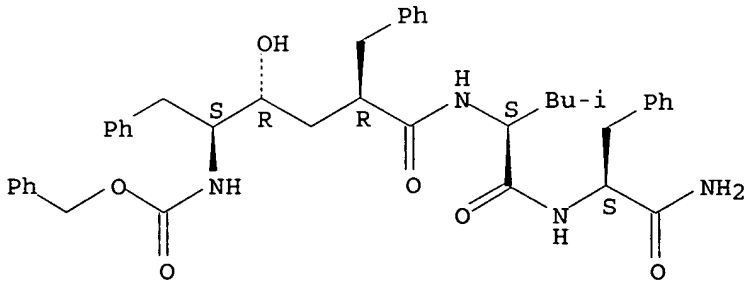
RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



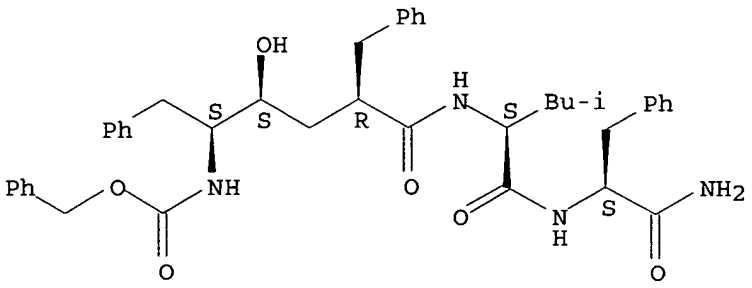
RN 350981-88-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-4-hydroxy-1-oxo-6-phenyl-5-[[(phenylmethoxy)carbonyl]amino]-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **126409-32-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptide derivs. as γ-secretase inhibitors)
RN 126409-32-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-4-hydroxy-1-oxo-6-phenyl-5-[[(phenylmethoxy)carbonyl]amino]-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

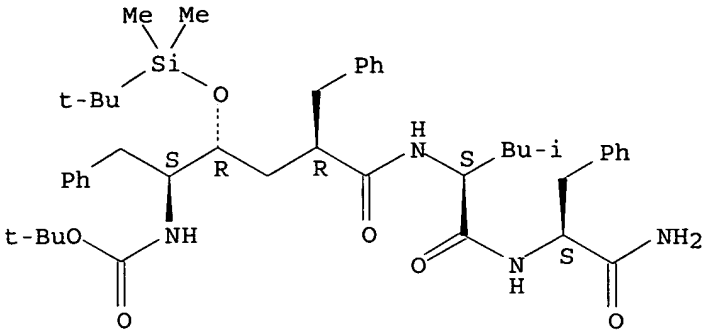
Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

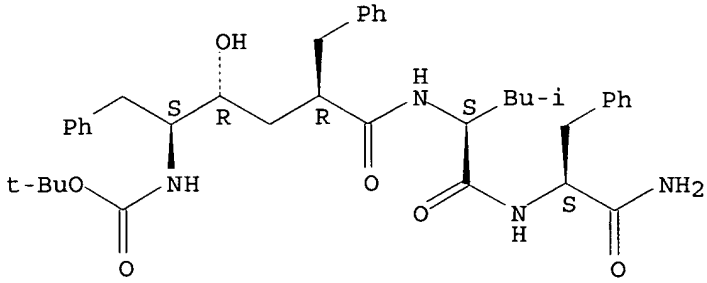
L5 ANSWER 18 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:155242 HCAPLUS
DOCUMENT NUMBER: 134:340687
TITLE: A stereocontrolled synthesis of 2R-benzyl-5S-tert-butoxycarbonylamino-4R-(tert-butyldimethylsilanyloxy)-6-phenyl-hexanoic acid (Phe-Phe hydroxyethylene dipeptide isostere)
AUTHOR(S): Nadin, A.; Sanchez Lopez, J. M.; Neduvelil, J. G.; Thomas, S. R.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, The Neuroscience Research Centre, Harlow, Essex, CM20 2QR, UK
SOURCE: Tetrahedron (**2001**), 57(9), 1861-1864
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:340687
AB 2R-Benzyl-5S-tert-butoxycarbonylamino-4R-(tert-butyldimethylsilanyloxy)-6-phenyl-hexanoic acid, a hydroxyethylene dipeptide isostere corresponding to Phe-Phe, has been synthesized in a practical, stereocontrolled fashion from (L)-phenylalanine.
IT **338801-69-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereocontrolled synthesis of benzyltertbutoxycarbonylaminotertbutyldimethylsilanyloxyphenylhexanoic acid)
RN 338801-69-7 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **292632-98-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereocontrolled synthesis of benzyltertbutoxycarbonylaminotertbutyldimethylsilanyloxyphenylhexanoic acid)
RN 292632-98-5 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:455820 HCAPLUS
DOCUMENT NUMBER: 133:234317
TITLE: L-685,458, an Aspartyl Protease Transition State Mimic, Is a Potent Inhibitor of Amyloid β-Protein Precursor γ-Secretase Activity
AUTHOR(S): Shearman, Mark S.; Beher, Dirk; Clarke, Earl E.; Lewis, Huw D.; Harrison, Tim; Hunt, Peter; Nadin, Alan; Smith, Adrian L.; Stevenson, Graeme; Castro, Jose L.
CORPORATE SOURCE: Departments of Molecular Biology and Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories The Neuroscience Research Centre, Harlow, CM20 2QR, UK
SOURCE: Biochemistry (**2000**), 39(30), 8698-8704
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Progressive cerebral amyloid β-protein (Aβ) deposition is believed to play a central role in the pathogenesis of Alzheimer's disease

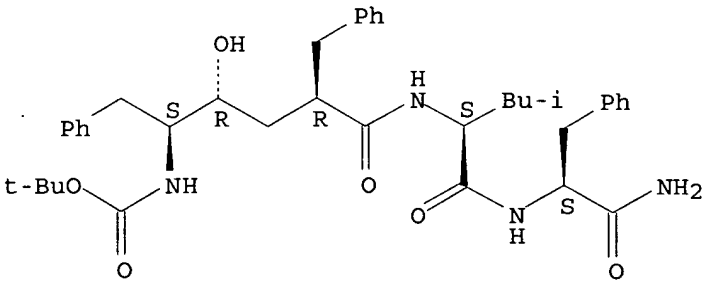
(AD). Elevated levels of Aβ(42) peptide formation have been linked to early-onset familial AD-causing gene mutations in the amyloid β-protein precursor (AβPP) and the presenilins. Sequential cleavage of AβPP by the β- and γ-secretases generates the N- and C-termini of the Aβ peptide, making both the β- and γ-secretase enzymes potential therapeutic targets for AD. The identity of the AβPP γ-secretase and the mechanism by which the C-termini of Aβ are formed remain uncertain, although it has been suggested that the presenilins themselves are novel intramembrane-cleaving γ-secretases of the aspartyl protease class. In this study we report the identification of L-685,458 as a structurally novel inhibitor of AβPP γ-secretase activity, with a similar potency for inhibition of Aβ(42) and Aβ(40) peptides. This compound contains an hydroxyethylene dipeptide isostere which suggests that it could function as a transition state analog mimic of an aspartyl protease. The preferred stereochem. of the hydroxyethylene dipeptide isostere was found to be the opposite to that required for inhibition of the HIV-1 aspartyl protease, a factor which may contribute to the observed specificity of this compound Specific and potent inhibitors of AβPP γ-secretase activity such as L-685,458 will enable important advances toward the identification and elucidation of the mechanism of action of this enigmatic protease.

IT **292632-98-5**, L 685458
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(L-685,458, an aspartyl proteinase transition state mimic, is a potent inhibitor of amyloid β-protein precursor γ-secretase activity)

RN 292632-98-5 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

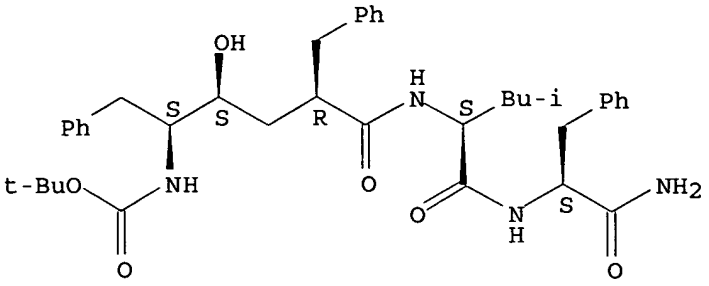


IT **126409-24-3**, L 682679 **292620-20-3**, L 684414
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison; L-685,458, an aspartyl proteinase transition state mimic, is a potent inhibitor of amyloid β-protein precursor γ-secretase activity)

RN 126409-24-3 HCAPLUS

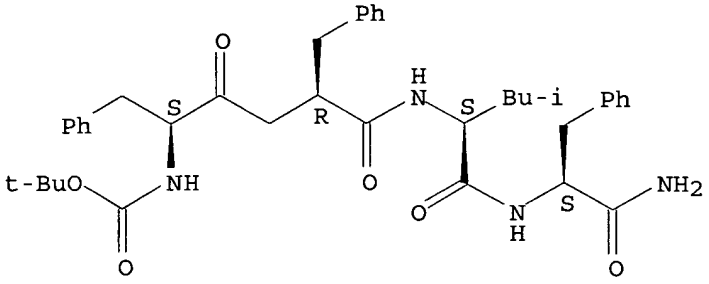
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 292620-20-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-1,4-dioxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

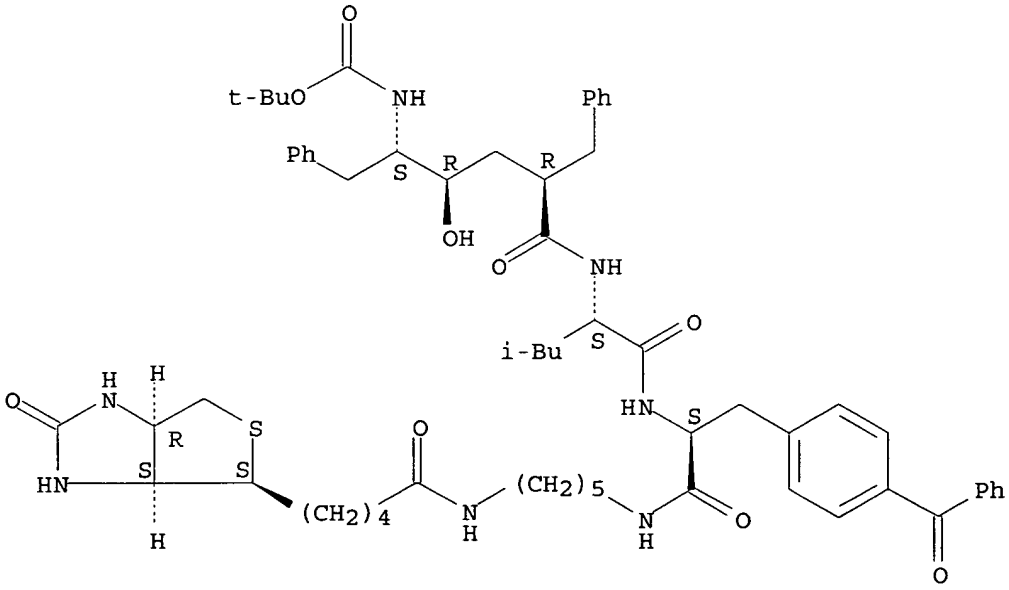
L5 ANSWER 20 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:435380 HCAPLUS
DOCUMENT NUMBER: 133:173892
TITLE: Photoactivated γ-secretase inhibitors directed to the active site covalently label presenilin 1
AUTHOR(S): Li, Yue-Ming; Xu, Min; Lai, Ming-Tain; Huang, Qlan; Castro, Jose L.; Dimuzio-Mower, Jillian; Harrison, Timothy; Lellis, Colin; Nadin, Alan; Neduvelil, Joseph G.; Register, R. Bruce; Sardana, Mohinder K.; Shearman, Mark S.; Smith, Adrian L.; Shi, Xiao-Ping; Yin, Kuo-Chang; Shafer, Jules A.; Gardell, Stephen J.
CORPORATE SOURCE: Department of Biological Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Nature (London) (**2000**), 405(6787), 689-694
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:173892
AB Cleavage of the amyloid precursor protein (APP) by β- and γ-secretases generates the N- and C-termini, resp., of Aβ amyloidogenic peptides Aβ40 and Aβ42, the major constituents of the amyloid plaques in the brain parenchyma of Alzheimer's disease patients. There is evidence that the polytopic membrane-spanning proteins, presenilin 1 and 2 (PS1 and PS2), are important determinants of γ-secretase activity: (1) mutations in PS1 and PS2 that are associated with early-onset familial Alzheimer's disease increase the production of Aβ42, the more

amyloidogenic peptide; (2) γ-secretase activity is reduced in neuronal cultures derived from PS1-deficient mouse embryos; and (3) directed mutagenesis of 2 conserved Asp residues in transmembrane segments of PS1 inactivates the ability of γ-secretase to catalyze processing of APP within its transmembrane domains. It is unknown, however, whether PS1 (which has little or no homol. to any known aspartyl protease) is itself a transmembrane aspartic protease or a γ-secretase cofactor, or helps to colocalize γ-secretase and APP. Here, the authors report photoaffinity labeling of PS1 (and PS2) by potent γ-secretase inhibitors that were designed to function as transition state analog inhibitors directed to the active site of an aspartic protease. This observation indicates that PS1 (and PS2) may contain the active site of γ-secretase. Interestingly, the intact, single-chain form of wild-type PS1 was not labeled by an active site-directed photoaffinity probe, suggesting that intact wild-type PS1 may be an aspartic protease zymogen.

IT **288290-54-0P**, L 852505 **288290-55-1P**, L 852646
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(photoactive γ-secretase inhibitor; preparation of photoactive γ-secretase inhibitors)

RN 288290-54-0 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-4-benzoyl-N-[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]- (9CI) (CA INDEX NAME)

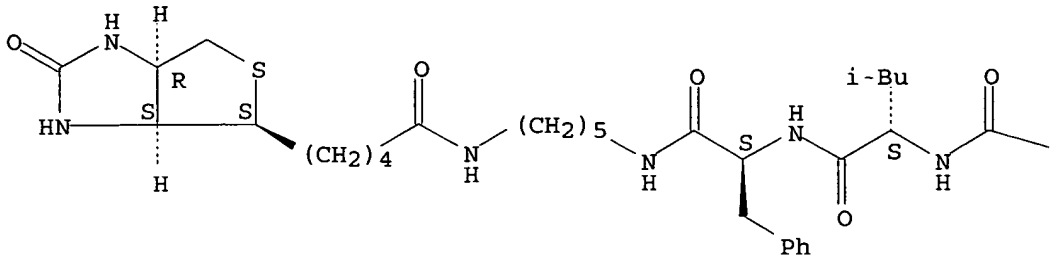
Absolute stereochemistry.



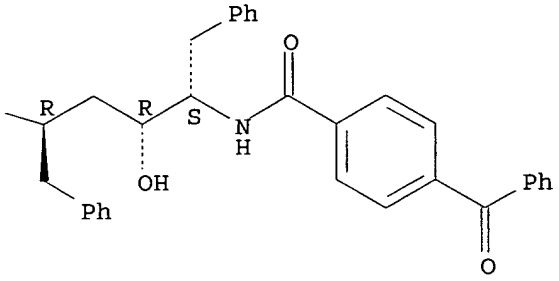
RN 288290-55-1 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[(4-benzoylbenzoyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-N-[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



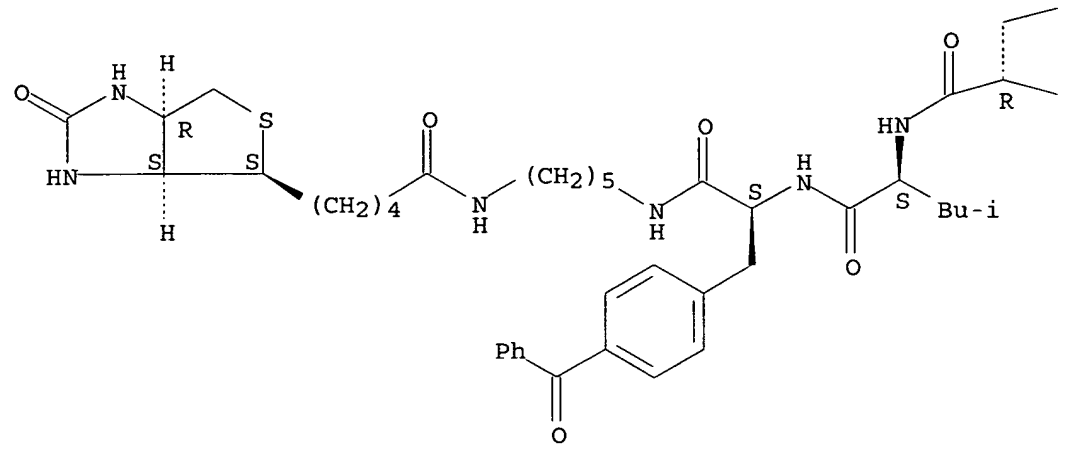
IT **288259-38-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of photoactive γ-secretase inhibitors)

RN 288259-38-1 HCAPLUS

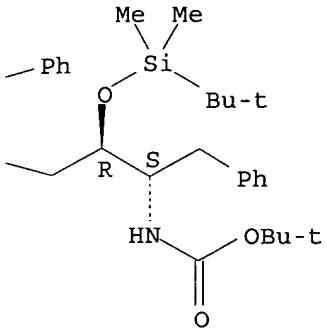
CN L-Phenylalaninamide, N-[(2R,4R,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-4-benzoyl-N-[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]pentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:71255 HCAPLUS
DOCUMENT NUMBER: 128:154218
TITLE: Synthesis of silanol-based peptide analogs and their use to inhibit protease enzymes
INVENTOR(S): Sieburth, Scott M.; Mutahi, Alfred M.
PATENT ASSIGNEE(S): Research Foundation of State University of New York, USA; Sieburth, Scott M.; Mutahi, Alfred M.
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9802578	A1	19980122	WO 1997-US12041	19970711 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5760019	A	19980602	US 1996-680330	19960712 <--
CA 2258685	AA	19980122	CA 1997-2258685	19970711 <--
AU 9737240	A1	19980209	AU 1997-37240	19970711 <--
AU 717621	B2	20000330		
EP 1019533	A1	20000719	EP 1997-934103	19970711 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000515513	T2	20001121	JP 1998-506152	19970711 <--
US 6441212	B1	20020827	US 1998-194715	19981217 <--
US 2003096793	A1	20030522	US 2002-171560	20020611 <--

PRIORITY APPLN. INFO.:	US 1996-680330	A2	19960712
	WO 1997-US12041	W	19970711
	US 1998-194715	A3	19981217

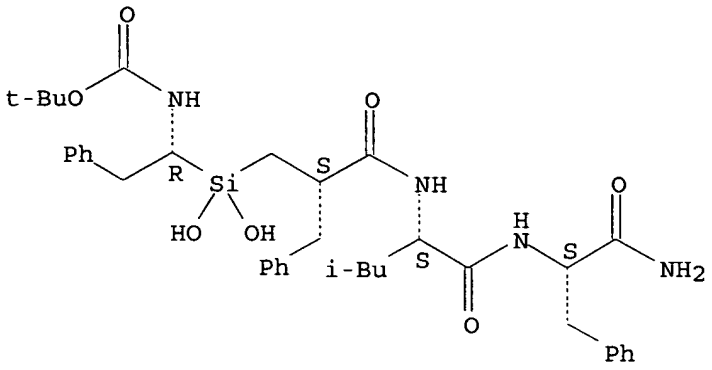
AB Silanol compds. of formula SiXYAB (I), (-ABSiO-)n (II), or ZO(-ABSiO-)nZ' (III), wherein X is OH; Y is OH, H, lower alkyl of one to six carbons or heteroatoms or F; Z and Z' are independently H, lower alkyl or Q3Si where Q is lower alkyl or aryl; n is 3-50; n' is 2-50; A and B are independently (a) alkyl of one to ten carbons or heteroatoms, (b) aryl of four to ten carbons or heteroatoms, (c) cyclic of three to ten carbons or heteroatoms, or moieties of the formulas CHR1CHR2C(O)NR3R4 (d), CHR5NR6R7 (e), or CHR8CHR9NR10R11 (f); R1-R11 groups are each independently H, alkyl of one to ten carbons or heteroatoms, aryl of 4 to 14 carbons or heteroatoms, arylalkyl of five to twenty carbons or heteroatoms; unsubstituted carbonyl or substituted carbonyl. Heteroatoms are N, O, Si or S. At least one of A or B, or both A and B are d, e, or f. Silanols I inhibit protease enzymes and can be used as pharmaceuticals.

IT **202743-67-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protease enzyme inhibitory activity of)

RN 202743-67-7 HCAPLUS

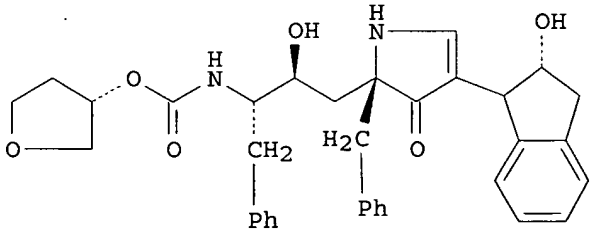
CN L-Phenylalaninamide, N-[(2S)-2-[[[(1R)-1-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]dihydroxysilyl]methyl]-1-oxo-3-phenylpropyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:528483 HCAPLUS
DOCUMENT NUMBER: 127:130483
TITLE: An Orally Bioavailable Pyrrolinone Inhibitor of HIV-1 Protease: Computational Analysis and X-ray Crystal Structure of the Enzyme Complex
AUTHOR(S): Smith, Amos B., III; Hirschmann, Ralph; Pasternak, Alexander; Yao, Wenquing; Sprengeler, Paul A.; Holloway, M. Katharine; Kuo, Lawrence C.; Chen, Zhongguo; Darke, Paul L.; Schleif, William A.
CORPORATE SOURCE: Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Journal of Medicinal Chemistry (**1997**), 40(16), 2440-2444
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The design and synthesis of HIV-1 protease inhibitors based upon the 2,5,5-trisubstituted pyrrolin-4-one scaffold are described. Reduced mol. wts. compared with our earlier bispyrrolinones, were expected to result in improved pharmacokinetic properties. Indeed, though less active than analogous amide-based inhibitors against the purified enzyme, the monopyrrolinones possess superior cellular transport properties as indicated by lower CIC95/IC50 ratios. The most potent inhibitor (I)

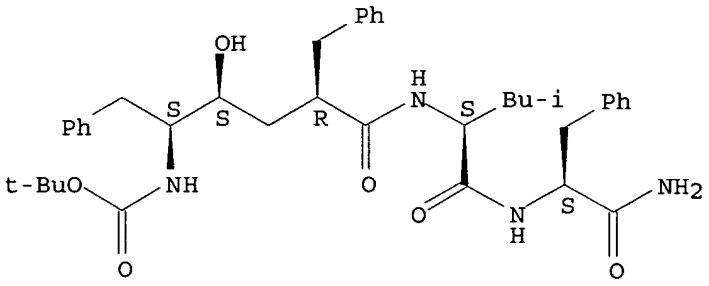
displayed 13% oral bioavailability in dogs. X-ray anal. of I cocrystd. with the enzyme revealed an unexpected H-bond to Asp25 as well as binding of a water mol. in the active site. Comparison with the similar complex of the amide inhibitor Crixivan showed displacement of the protease backbone to accommodate the pyrrolinone ring, accompanied by variation in H-bonding and more subtle conformational changes in other regions of the enzyme.

IT **126409-24-3**, L 682679
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally bioavailable pyrrolinone inhibitor of HIV-1 protease, with computational anal. and X-ray crystal structure of enzyme complex)

RN 126409-24-3 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

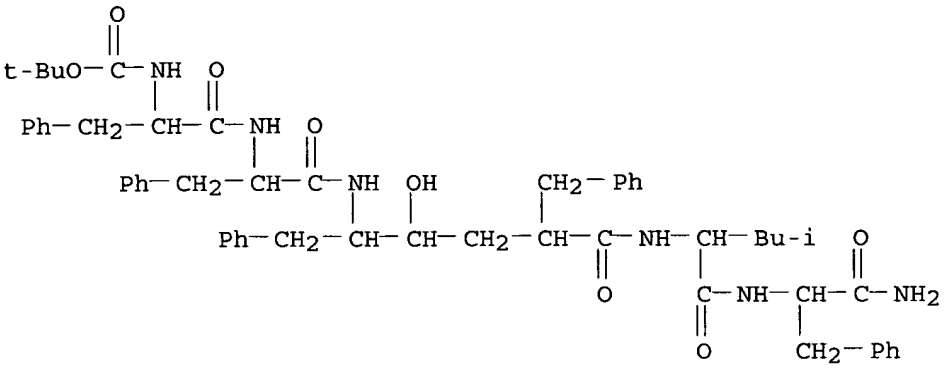


L5 ANSWER 23 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:139218 HCAPLUS
DOCUMENT NUMBER: 118:139218
TITLE: Structure-activity studies and antiviral properties of hydroxyethylene transition state inhibitors of HIV-1 protease
AUTHOR(S): Payne, L. S.; Young, S. D.; Lyle, T. A.; Wiscount, C. M.; Thompson, W. J.; Vacca, J. P.; Wiggins, J. M.; Gaffin, N.; Huff, J. R.; et al.
CORPORATE SOURCE: Dep. Med. Chem., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Pept.: Chem. Biol., Proc. Am. Pept. Symp., 12th (**1992**), Meeting Date 1991, 740-2. Editor(s): Smith, John A.; Rivier, Jean E. ESCOM: Leiden, Neth. CODEN: 57XGA9
DOCUMENT TYPE: Conference
LANGUAGE: English

AB This report describes some potent and effective HIV-1 protease (HIVP) inhibitors which emerged from the SAR studies through modification of a screening lead L-364,505, a heptapeptide renin inhibitor which contains a hydroxethylene transition state mimic. SAR led the authors to pseudotripeptide HIVP inhibitors devoid of renin inhibitory potency through optimization of P2 to P2' binding elements. SAR studies P1' and P2' are discussed.

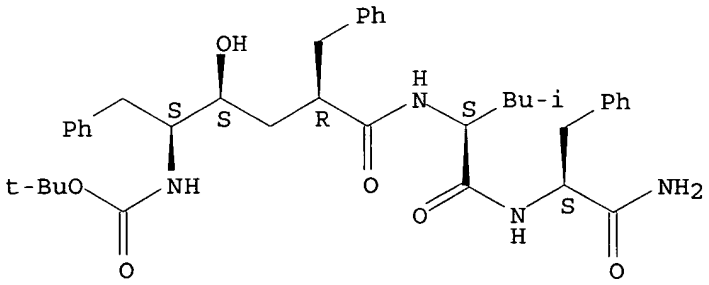
IT **98818-74-7 126409-24-3**
RL: BIOL (Biological study)
(HIV-1 protease inhibition by, structure in relation to)

RN 98818-74-7 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



RN 126409-24-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 24 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:449277 HCAPLUS
DOCUMENT NUMBER: 117:49277
TITLE: Preparation of peptides as drugs
INVENTOR(S): Dorsch, Dieter Dr; Raddatz, Peter Dr; Schmitges, Claus J.
PATENT ASSIGNEE(S): Merck Patent Gesellschaft Mit Beschraenkter Haftung, Germany
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 481311	A2	19920422	EP 1991-117014	19911005 <--
EP 481311	A3	19921119		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE

DE 4033062	A1	19920423	DE 1990-4033062	19901018 <--
AU 9185877	A1	19920430	AU 1991-85877	19911015 <--
CA 2053573	AA	19920419	CA 1991-2053573	19911016 <--
ZA 9108294	A	19920729	ZA 1991-8294	19911017 <--
JP 04316548	A2	19921106	JP 1991-333849	19911018 <--

PRIORITY APPLN. INFO.: DE 1990-4033062 A 19901018

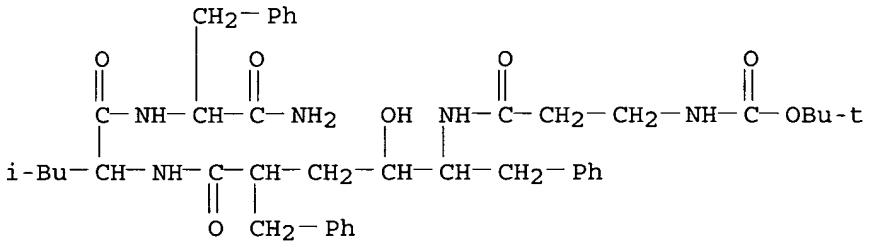
OTHER SOURCE(S): MARPAT 117:49277

AB Peptides X(NHCHR1CO)nNH(CH2)qCONHCHR2CR3CR4R5CHR6CO(NHCHR7CO)pWR8 [I; X = H, R9OCmH2mCO, R9CmH2mOCO, R9CmH2mCO, R9SO2, etc.; W = O, NH; R1, R2, R7-R9 = H, A, Ar, aralkyl, Het, Het-alkyl, (substituted) C3-7 cycloalkyl, C4-11 cycloalkylalkyl, etc.; R3 = (H, OH), (H, NH2), O; R4, R5 = H, A; R6 = aralkyl, C4-11 cycloalkylalkyl; q = 2, 3; m = 0-10; n, p = 0-3; Ar = (substituted) Ph, naphthyl; Het = 5- or 6-membered (substituted) heterocyclyl containing 1-4 N, O or S atoms which may be fused with a benzene ring, including N- or S-oxides; A = C1-8 alkyl] were prepared for control of renin-induced hypertension, aldosteronism and retroviral diseases (no data). Thus Boc-β-Ala-OH was condensed with H-ABHP-Leu-Phe-NH2 (ABHP = 5S-amino-2R-benzyl-4S-hydroxy-6-phenylhexanoic acid residue) in CH2Cl2 containing N-methylmorpholine, HOBt, and DCC at 0-5° to give Boc-β-Ala-ABHP-Leu-Phe-NH2. Formulations containing I are given.

IT **142257-60-1P 142257-63-4P 142293-59-2P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as drug)

RN 142257-60-1 HCAPLUS

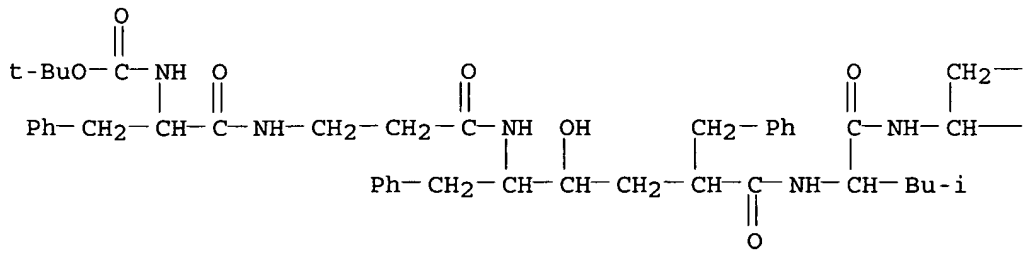
CN L-Phenylalaninamide, N-[5-[[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxopropyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



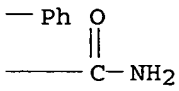
RN 142257-63-4 HCAPLUS

CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-β-alanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)

PAGE 1-A

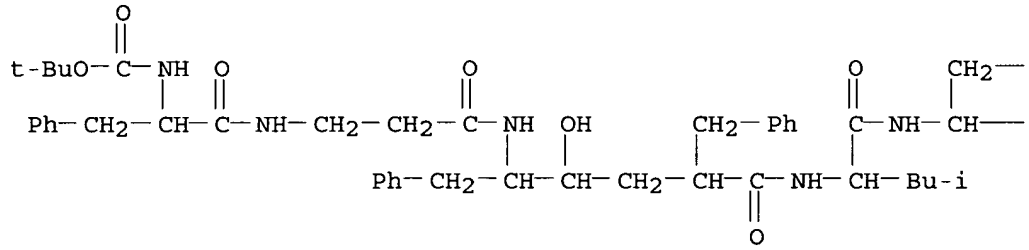


PAGE 1-B

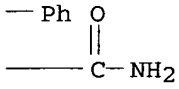


RN 142293-59-2 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-β-alanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4R*,5R*)]- (9CI) (CA INDEX NAME)

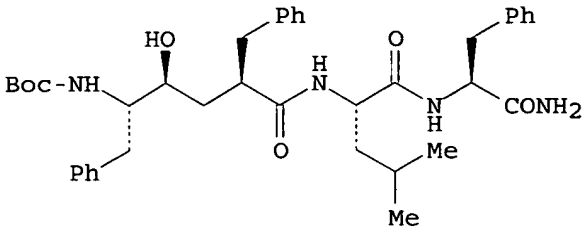
PAGE 1-A



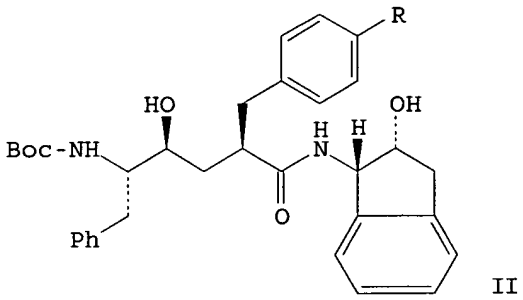
PAGE 1-B



L5 ANSWER 25 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:408413 HCAPLUS
DOCUMENT NUMBER: 117:8413
TITLE: HIV-1 protease inhibitors based on hydroxyethylene dipeptide isosteres: An investigation into the role of the P1' side chain on structure-activity
AUTHOR(S): Young, Steven D.; Payne, Linda S.; Thompson, Wayne J.; Gaffin, Neil; Lyle, Terry A.; Britcher, Susan F.; Graham, Samuel L.; Schultz, Thomas H.; Deana, Albert A.; et al.
CORPORATE SOURCE: Dep. Med. Chem., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Medicinal Chemistry (**1992**), 35(10), 1702-9
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 117:8413
GI



I



II

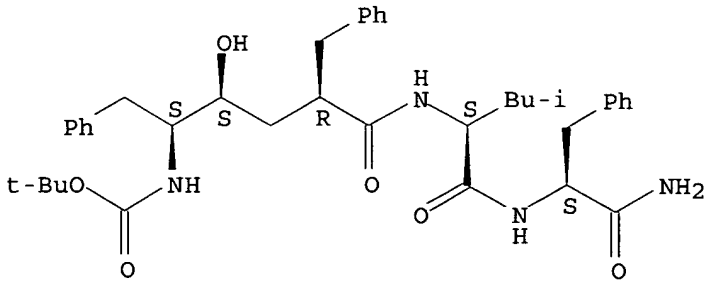
AB A systematic investigation was undertaken to determine the role of the P1' side chain in a series of hydroxyethylene isostere based inhibitors of HIV-1 protease. Substitution and homologation of the benzyl P1' side chain of the Phe-Phe isostere based pseudopeptides I (Boc = Me3CO2C) (L-682,679) and II (R = H) (L-685,434) with various heteroalkyl groups leads to a series of extremely potent inhibitors of the enzyme. Several examples of the most potent inhibitors were very effective in ex vivo cell based viral spread assay using human H9 T-lymphocytes and the the IIIb isolate of HIV-1. Compound II [R =(CH2)3OH] is 120 times more potent than I and 16 times more potent than II (R = H) in inhibiting the spread of infection in this assay.

IT **126409-24-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(inhibition by, of human immunodeficiency virus-1 protease)

RN 126409-24-3 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

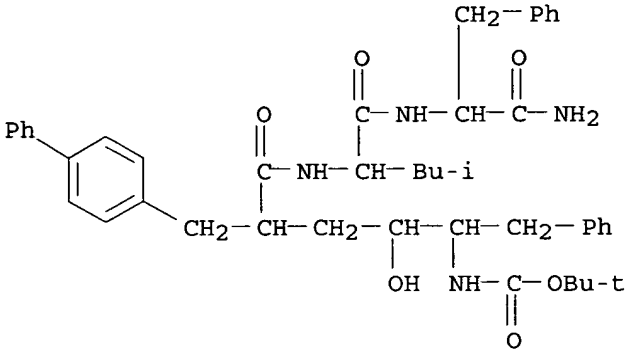
Absolute stereochemistry.



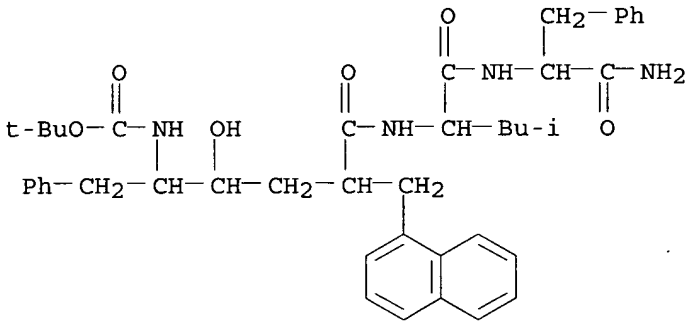
IT **126409-51-6P 141221-98-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 126409-51-6 HCAPLUS

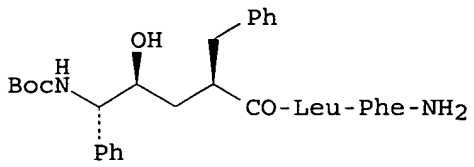
CN L-Phenylalaninamide, N-[(2R,4S,5S)-2-([1,1'-biphenyl]-4-ylmethyl)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenylhexyl]-L-leucyl- (9CI) (CA INDEX NAME)



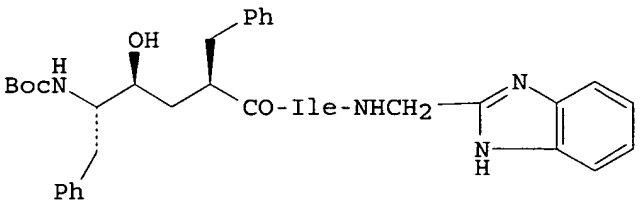
RN 141221-98-9 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-2-(1-naphthalenylmethyl)-1-oxo-6-phenylhexyl]-L-leucyl- (9CI) (CA INDEX NAME)



L5 ANSWER 26 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:608499 HCAPLUS
DOCUMENT NUMBER: 115:208499
TITLE: Design and synthesis of HIV protease inhibitors. Variations of the carboxyterminus of the HIV protease inhibitor L-682,679
AUTHOR(S): DeSolms, S. Jane; Giuliani, Elizabeth A.; Guare, James P.; Vacca, Joseph P.; Sanders, William M.; Graham, Samuel L.; Wiggins, J. Mark; Darke, Paul L.; Sigal, Irving S.; et al.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Medicinal Chemistry (**1991**), 34(9), 2852-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 115:208499
GI



I



II

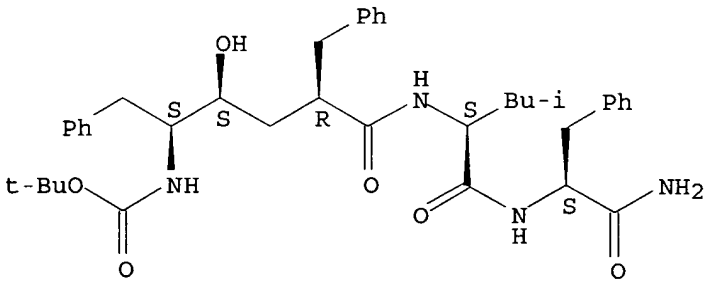
AB L-682,679 (I, Boc = Me3CO2C) tetrapeptide analogs, in which the carboxy terminus has been shortened and modified, were prepared and their inhibitory activity measured against the HIV protease in a peptide cleavage assay. Selected examples were tested as inhibitors of virus spread in cell culture. Analog II was a 10-fold more potent enzyme inhibitor than I in vitro and 30-fold more potent in inhibiting the viral spread in cells.

IT **126409-24-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and HIV protease-inhibiting activity of)

RN 126409-24-3 HCAPLUS

CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



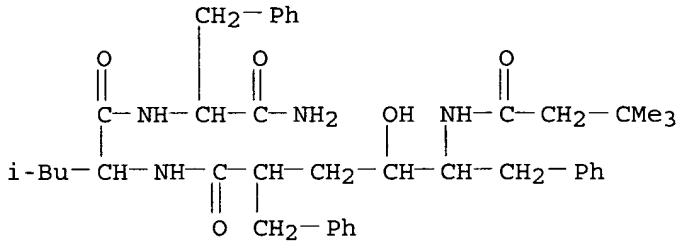
L5 ANSWER 27 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:138698 HCAPLUS
DOCUMENT NUMBER: 114:138698
TITLE: L-687,908, a potent hydroxyethylene containing HIV protease inhibitor
AUTHOR(S): Vacca, Joseph P.; Guare, J. P.; DeSolms, S. J.; Sanders, W. M.; Giuliani, E. A.; Young, S. D.; Darke, P. L.; Sigal, I. S.; Schleif, W. A.; et al.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Medicinal Chemistry (**1991**), 34(3), 1225-8

CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 114:138698

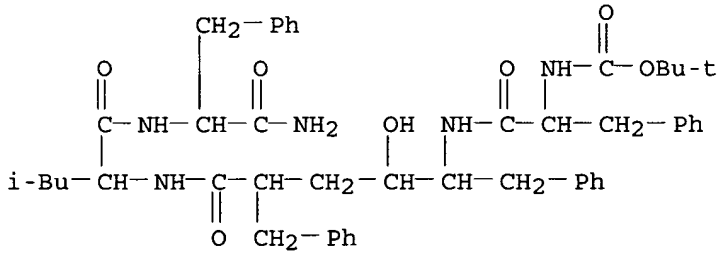
AB L-364,505 [(I), X = PhePhe, R = CH2Ph, AA = Leu-Phe-NH2] (II) was found to be a potent inhibitor of HIV-1 protease in vitro but had modest activity in preventing the spread of HIV infection in H9 cell culture. Deletion of the Phe-Phe group of II led to to L-682,679 [I, X = bond, R = CH2Ph, AA = Leu-Phe-NH2] (III) which had a similar IC50 to II but was greater than 10 times as active as II toward inhibiting the spread of infection in H9 cells. Further modification of compound III in which the P1', P2', and P3' sites were modified led to compound (L-687,908 I, X = bond, R = 3-phenyl-2-propenyl, AA = isoleucyl-2-aminomethylbenzimidazole) (IV) which was a very potent inhibitor of HIV-1 protease in vitro and in cell culture. The synthesis and structure activity relationships of III analogs which led to the discovery of IV are presented.

IT **129252-79-5 132565-30-1**
RL: BIOL (Biological study)
(HIV protease inhibition by)

RN 129252-79-5 HCAPLUS
CN L-Phenylalaninamide, N-[5-[(3,3-dimethyl-1-oxobutyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



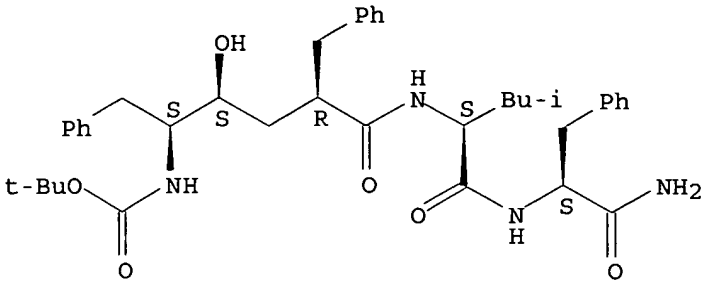
RN 132565-30-1 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxo-3-phenylpropyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-[2R*,4S*,5S*(S*)]]- (9CI) (CA INDEX NAME)



IT **126409-24-3**, L 682679
RL: BIOL (Biological study)
(deprotection and HIV protease inhibition by)

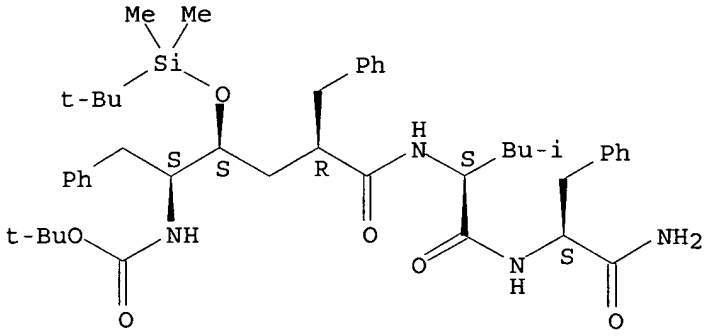
RN 126409-24-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

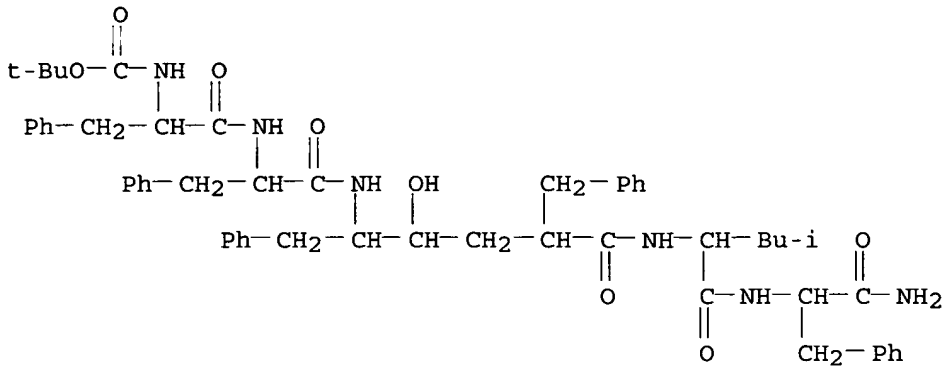


IT **126410-32-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and desilylation of)
RN 126410-32-0 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **98818-74-7P**, L 364505
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as HIV protease inhibitor)
RN 98818-74-7 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)

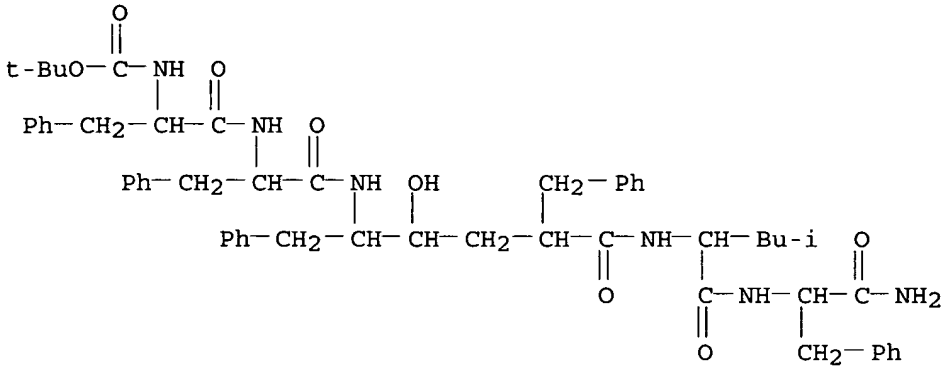


L5 ANSWER 28 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:565407 HCAPLUS
DOCUMENT NUMBER: 113:165407
TITLE: Renin inhibitors useful for the treatment of AIDS by inhibition of human immunodeficiency virus (HIV) protease
INVENTOR(S): Sigal, Irving S.; Huff, Joel R.; Darke, Paul L.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 36 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
EP 357332	A2	19900307	EP 1989-308551		19890823	<--
EP 357332	A3	19910731				
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE						
DK 8904143	A	19900226	DK 1989-4143		19890823	<--
JP 02117615	A2	19900502	JP 1989-216193		19890824	<--
PRIORITY APPLN. INFO.:			US 1988-235841	A	19880824	
			US 1989-328644	A	19890328	

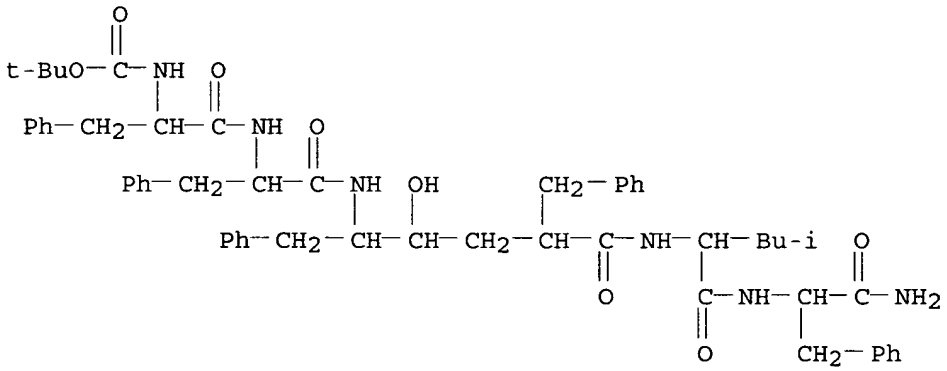
OTHER SOURCE(S): MARPAT 113:165407
AB The title renin inhibitors are substituted peptide derivs. (Markush structures given) and their pharmaceutically acceptable salts. Thus, N'-(1,1-dimethylethoxycarbonyl)-Phe-Phe-5(S)-amino-4(S)-hydroxy-6-phenyl-2-(S or R)-(phenylmethyl)hexanoyl-Leu-Phe-amide (I) was synthesized and tested as an HIV protease inhibitor. At 0.1-100 μM, I showed 100% inhibition of a synthetic viral protease (amino acid residues 69-167 of the pol open reading frame) against an octapeptide substrate; I also was an inhibitor of the synthetic protease using β-casein as substrate. When H9 T-lymphoid cells persistently infected with the HTLV-IIIB isolate of HIV were incubated with I, the p55 gag precursor accumulated, as did 2 processing intermediates of 49 and 41 kilodaltons, relative to the p24 product. Using immunofluorescence, I was shown to reduce the spread of the above HIV isolate in cultures of MT-4 T-lymphoid cells.
IT **98818-73-6 98818-74-7 129729-73-3**
129729-74-4
RL: BIOL (Biological study)
(human immunodeficiency virus protease inhibition with)
RN 98818-73-6 HCAPLUS

CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4R*,5R*)]- (9CI) (CA INDEX NAME)



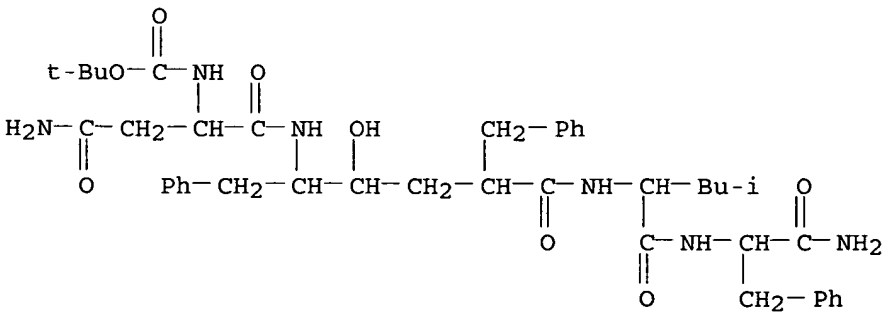
RN 98818-74-7 HCAPLUS

CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)

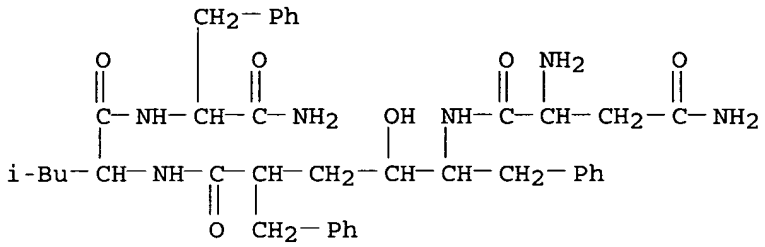


RN 129729-73-3 HCAPLUS

CN L-Phenylalaninamide, N-[5-[[4-amino-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1,4-dioxobutyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-[2R*,4S*,5S*(S*)]]- (9CI) (CA INDEX NAME)



RN 129729-74-4 HCAPLUS
CN L-Phenylalaninamide, N-[5-[(2,4-diamino-1,4-dioxobutyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-[2R*,4S*,5S*(S*)]]- (9CI) (CA INDEX NAME)



L5 ANSWER 29 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:532826 HCAPLUS
DOCUMENT NUMBER: 113:132826
TITLE: Preparation of peptides as HIV protease inhibitors for treatment of AIDS
INVENTOR(S): Desolms, S. Jane; Huff, Joel R.; Vacca, Joseph P.; Sigal, Irving S.; Darke, Paul L.; Young, Steven D.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 72 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
EP 356223	A2	19900228	EP 1989-308555		19890823	<--
EP 356223	A3	19910821				
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE						
FI 8903962	A	19900225	FI 1989-3962		19890823	<--
DK 8904141	A	19900226	DK 1989-4141		19890823	<--
NO 8903400	A	19900226	NO 1989-3400		19890823	<--
ZA 8906430	A	19900530	ZA 1989-6430		19890823	<--
AU 8940192	A1	19900621	AU 1989-40192		19890823	<--
JP 02152949	A2	19900612	JP 1989-216192		19890824	<--
PRIORITY APPLN. INFO.:			US 1988-236495	A	19880824	
			US 1989-328645	A	19890328	

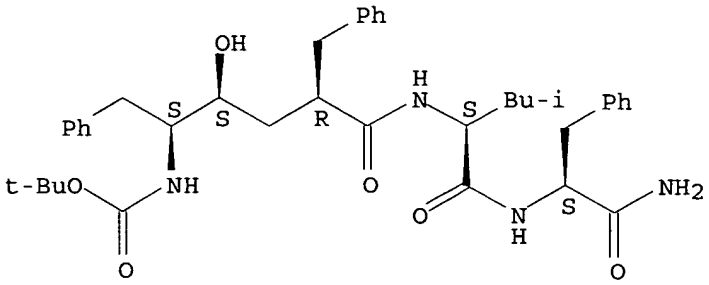
OTHER SOURCE(S): MARPAT 113:132826
AB A-G-B1-B2-J [I; A = alkanoyl, heterocyclylcarbonyl, etc.; G = (substituted) HNCH2CH(OH)CH2CH2C(Z) and similar dipeptide isosteres; Z = O, S, NH; B1, B2 = (substituted) NHCH2C(Z) or may be absent; J = OH, (substituted) NH2, alkoxy] and their pharmaceutically acceptable salts were prepared Condensation of [[5(S)-amino-4(S)-hydroxy-6-phenyl-2(R)-(phenylmethyl)hexanoyl]leucyl]phenylalaninamide (11-step preparation given) with 2-thiophenecarboxylic acid gave I [A = thiophene-2-carbonyl, G = (5S,4S,2R)-NHCH(CH2Ph)CH(OH)CH2CH(CH2Ph)CO, B1 = Leu, B2 = Phe, J = NH2], which had an IC50 of 11 nM against synthetic HIV protease.
IT **126409-24-3P 126409-41-4P 126410-32-0P**
126410-35-3P 126456-46-0P 126456-47-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and reaction of, in preparation of AIDS protease inhibitor)

RN 126409-24-3 HCAPLUS

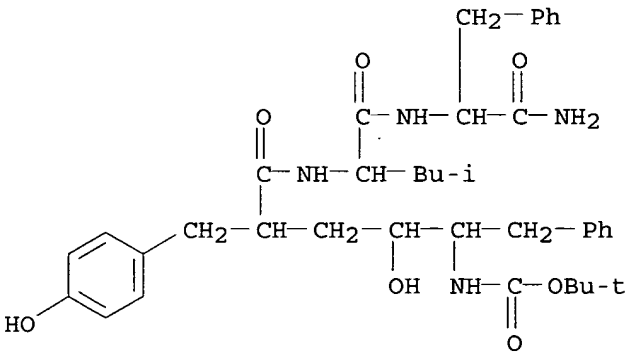
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 126409-41-4 HCAPLUS

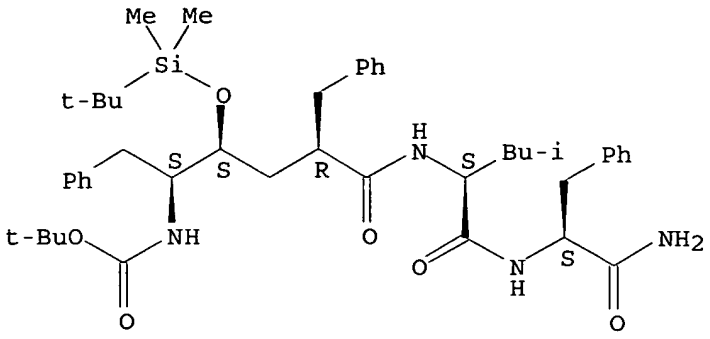
CN L-Phenylalaninamide, N-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-2-[(4-hydroxyphenyl)methyl]-1-oxo-6-phenylhexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



RN 126410-32-0 HCAPLUS

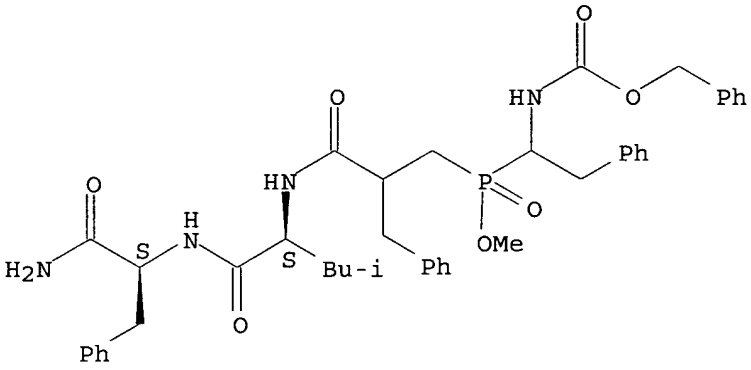
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

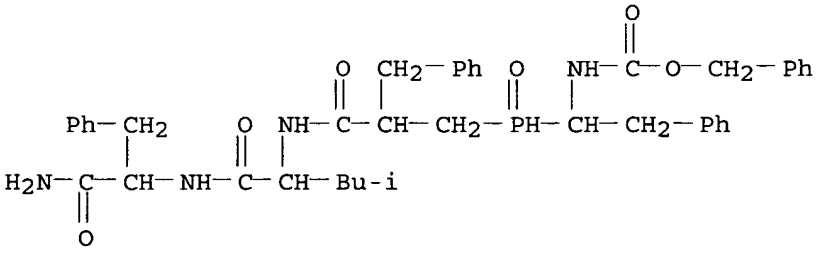


RN 126410-35-3 HCAPLUS
CN L-Phenylalaninamide, N-[2-[[methoxy[2-phenyl-1-[[(phenylmethoxy)carbonyl]amino]ethyl]phosphinyl]methyl]-1-oxo-3-phenylpropyl]-L-leucyl- (9CI) (CA INDEX NAME)

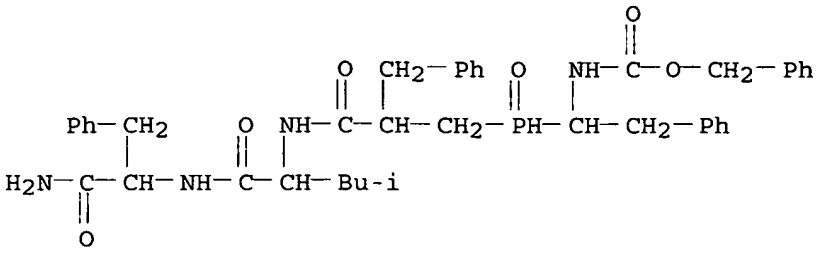
Absolute stereochemistry.



RN 126456-46-0 HCAPLUS
CN L-Phenylalaninamide, N-[1-oxo-2-(phenylmethyl)-3-[[2-phenyl-1-[[(phenylmethoxy)carbonyl]amino]ethyl]phosphinyl]propyl]-L-leucyl-, [2R-[2R*,3(1R*)]]- (9CI) (CA INDEX NAME)

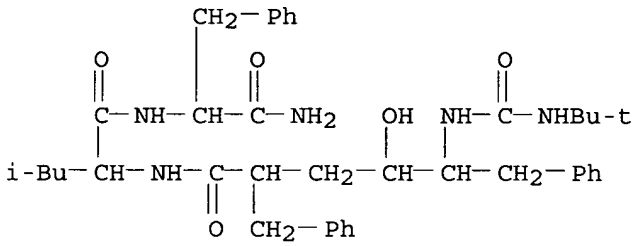


RN 126456-47-1 HCAPLUS
CN L-Phenylalaninamide, N-[1-oxo-2-(phenylmethyl)-3-[[2-phenyl-1-[[(phenylmethoxy)carbonyl]amino]ethyl]phosphinyl]propyl]-L-leucyl-, [2S-[2R*,3(1S*)]]- (9CI) (CA INDEX NAME)

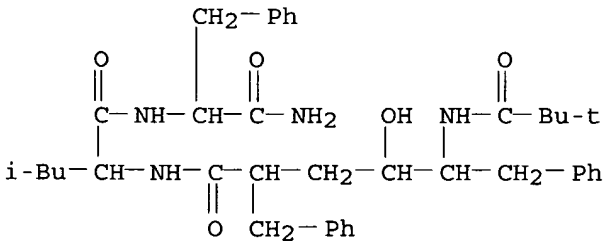


IT **129252-76-2P 129252-77-3P 129252-78-4P**
129252-79-5P 129252-80-8P 129252-89-7P
129252-91-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as AIDS protease inhibitor)

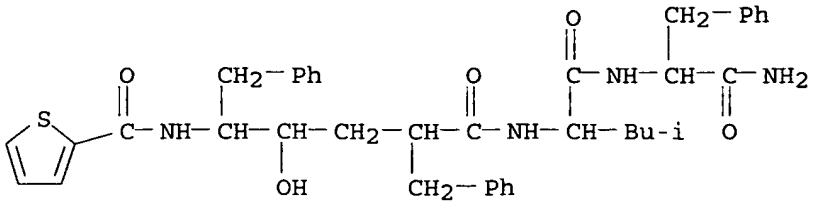
RN 129252-76-2 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



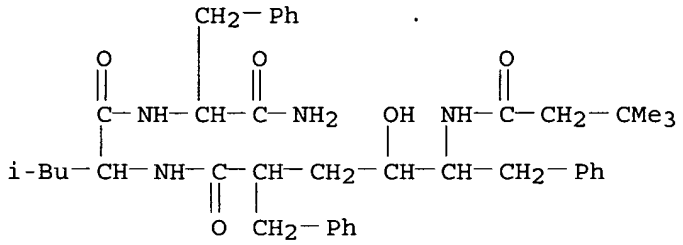
RN 129252-77-3 HCAPLUS
CN L-Phenylalaninamide, N-[5-[(2,2-dimethyl-1-oxopropyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



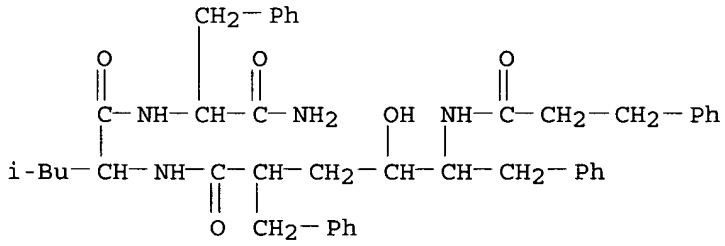
RN 129252-78-4 HCAPLUS
CN L-Phenylalaninamide, N-[4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)-5-[(2-thienylcarbonyl)amino]hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



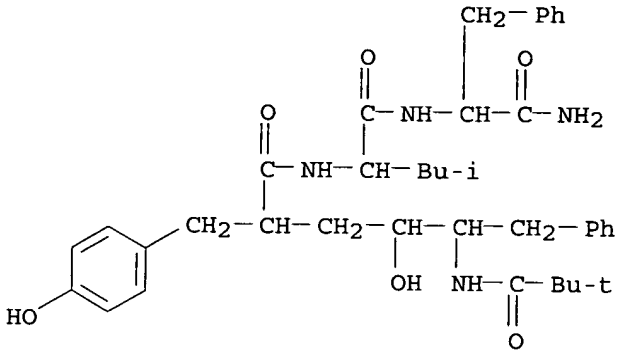
RN 129252-79-5 HCAPLUS
CN L-Phenylalaninamide, N-[5-[(3,3-dimethyl-1-oxobutyl)amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



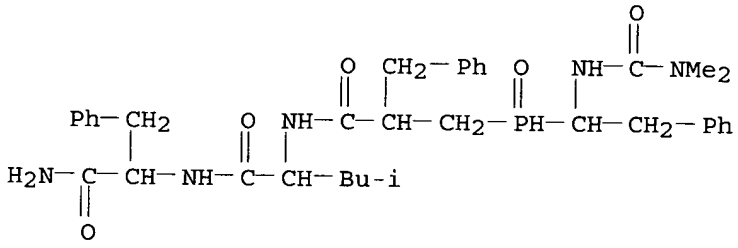
RN 129252-80-8 HCAPLUS
CN L-Phenylalaninamide, N-[4-hydroxy-1-oxo-5-[(1-oxo-3-phenylpropyl)amino]-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



RN 129252-89-7 HCAPLUS
CN L-Phenylalaninamide, N-[5-[(2,2-dimethyl-1-oxopropyl)amino]-4-hydroxy-2-[(4-hydroxyphenyl)methyl]-1-oxo-6-phenylhexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



RN 129252-91-1 HCAPLUS
CN L-Phenylalaninamide, N-[2-[[[1-[[(dimethylamino)carbonyl]amino]-2-phenylethyl]phosphinyl]methyl]-1-oxo-3-phenylpropyl]-L-leucyl-, stereoisomer (9CI) (CA INDEX NAME)



L5 ANSWER 30 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:199132 HCAPLUS
DOCUMENT NUMBER: 112:199132
TITLE: Preparation of human immunodeficiency virus (HIV) protease inhibitors for treatment of AIDS
INVENTOR(S): Sigal, Irving S.; Huff, Joel R.; Darke, Paul L.; Vacca, Joseph P.; Young, Steven D.; Desolms, S. Jane; Thompson, Wayne J.; Lyle, Terry A.; Graham, Samuel L.; Ghosh, Arun K.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 94 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 337714	A2	19891018	EP 1989-303539	19890411 <--
EP 337714	A3	19910807		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FI 8901716	A	19891013	FI 1989-1716	19890411 <--
NO 8901489	A	19891013	NO 1989-1489	19890411 <--
ZA 8902627	A	19891129	ZA 1989-2627	19890411 <--
DK 8901723	A	19891211	DK 1989-1723	19890411 <--

AU 8932706	A1	19891019	AU 1989-32706		19890412 <--
AU 620084	B2	19920213			
JP 02209854	A2	19900821	JP 1989-92762		19890412 <--
PRIORITY APPLN. INFO.:			US 1988-180507	A	19880412
			US 1988-236084	A	19880824
			US 1989-328643	A	19890328

OTHER SOURCE(S): MARPAT 112:199132

GI For diagram(s), see printed CA Issue.

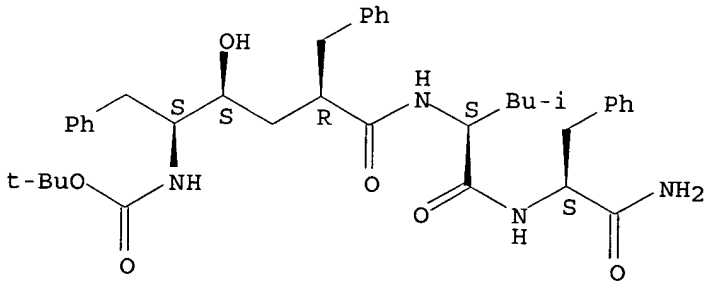
AB Dipeptides or amino acid amides or carboxamides A-G-B-B-J [I; A = Ph3C, H, CHO, (un)substituted C2-5 alkanoyl, phthaloyl, MeO2C, H2NOC(O), or arylsulfonylcarbamoyl, etc.; G = NHCHRCHR1QC(O), NHCHRQ1CHRC(:Z); Z = O, S, H2; R = H, OH, C1-4 alkoxy, NH2, etc.; R1 = OH, (un)substituted NH2; Q = (un)substituted C3-7 alicyclic, benzene, or 5- to 7-membered heterocyclic ring; Q1 = CH(OH)CHR, CH2NH, P(O)(OH)CH2, CH(OH), etc.; B = null, NHCHRC(:Z); J = OH, NH2, (un)substituted C1-6 alkoxy or C1-6 alkylamino, etc.], are prepared Thus, condensation of a hexanoic acid derivative (II; R2 = SiMe2CMe3, R3 = OH, BOC = Me3CO2C) (preparation given) with H-Leu-Phe-NH2.HCl.1/2H2O in the presence of 1-hydroxybenzotriazole.H2O, dimethyl-3-(3-dimethylaminopropyl)carbodiimide.HCl, and Et3N in DMF gave, after disilylation with Bu4NF in THF, II (R2 = H, R3 = Leu-Phe-NH2). The latter compound inhibited synthetic and Escherichia coli-expressed HIV protease with IC50 values of 2 and 0.6 nM, resp. Approx. 130 I were prepared

IT **126409-24-3P 126409-31-2P 126409-32-3P**
126409-34-5P 126409-36-7P 126409-41-4P
126409-51-6P 126409-54-9P 126409-79-8P
126438-21-9P 126456-46-0P 126456-47-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as HIV protease inhibitor for AIDS treatment)

RN 126409-24-3 HCAPLUS

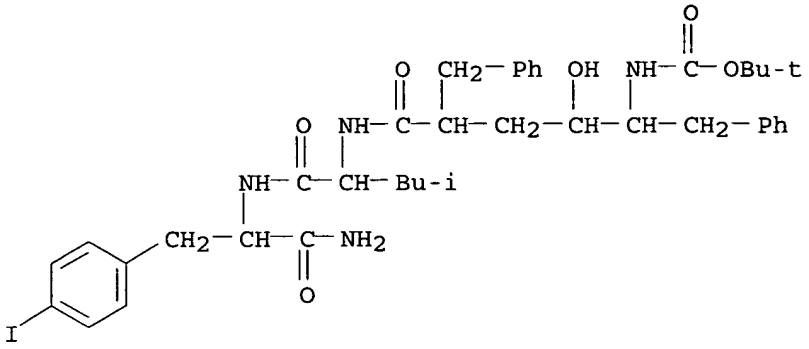
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



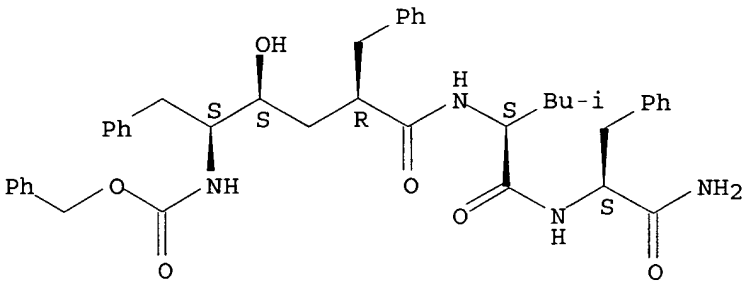
RN 126409-31-2 HCAPLUS

CN Phenylalaninamide, N-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-4-iodo-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



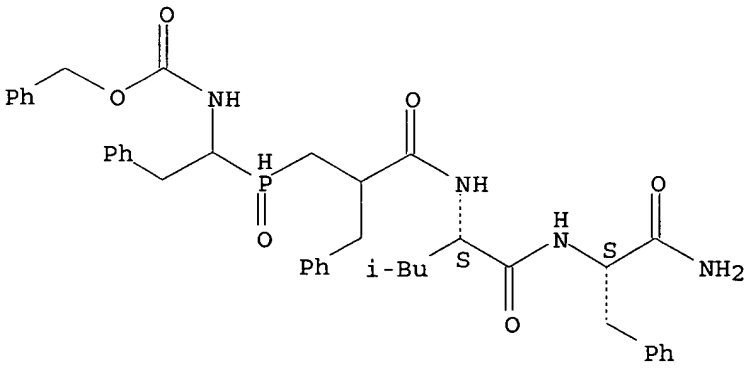
RN 126409-32-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-4-hydroxy-1-oxo-6-phenyl-5-[[(phenylmethoxy)carbonyl]amino]-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

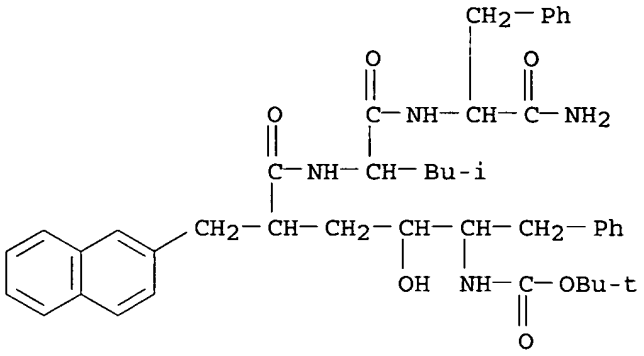


RN 126409-34-5 HCAPLUS
CN L-Phenylalaninamide, N-[1-oxo-2-(phenylmethyl)-3-[[2-phenyl-1-[[(phenylmethoxy)carbonyl]amino]ethyl]phosphinyl]propyl]-L-leucyl- (9CI) (CA INDEX NAME)

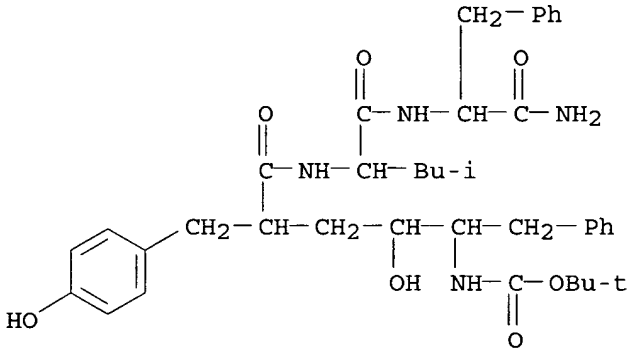
Absolute stereochemistry.



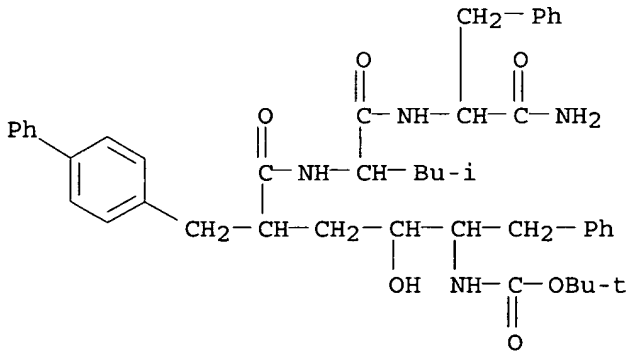
RN 126409-36-7 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-2-(2-naphthalenylmethyl)-1-oxo-6-phenylhexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



RN 126409-41-4 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-2-[(4-hydroxyphenyl)methyl]-1-oxo-6-phenylhexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)

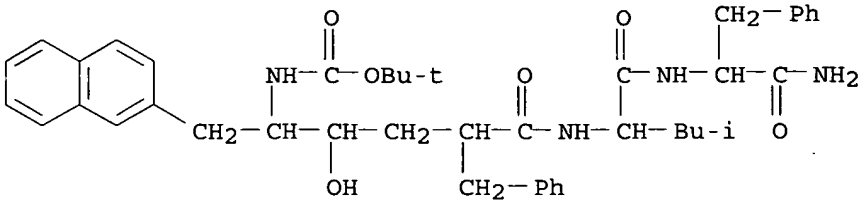


RN 126409-51-6 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-2-([1,1'-biphenyl]-4-ylmethyl)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenylhexyl]-L-leucyl- (9CI) (CA INDEX NAME)



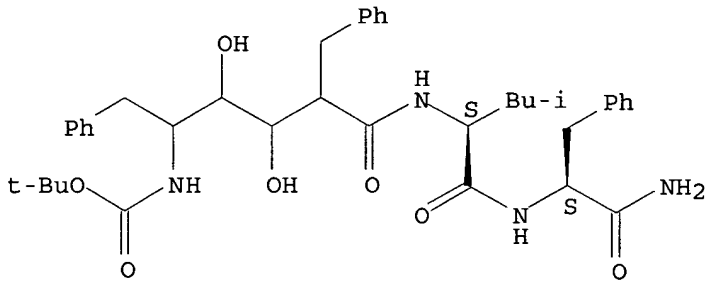
RN 126409-54-9 HCAPLUS

CN L-Phenylalaninamide, N-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-6-(2-naphthalenyl)-1-oxo-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)

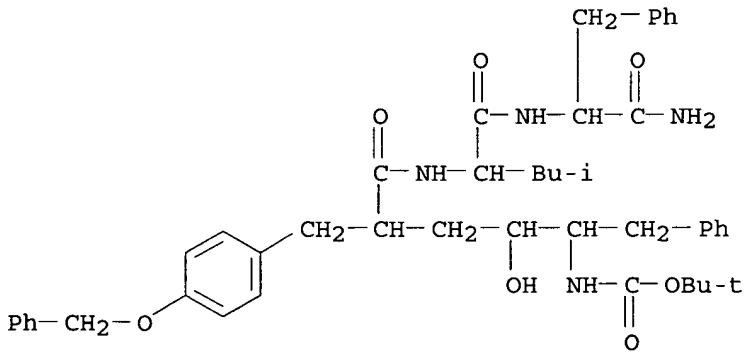


RN 126409-79-8 HCAPLUS
CN L-Phenylalaninamide, N-[2,5,6-trideoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-phenyl-2-(phenylmethyl)hexonoyl]-L-leucyl- (9CI) (CA INDEX NAME)

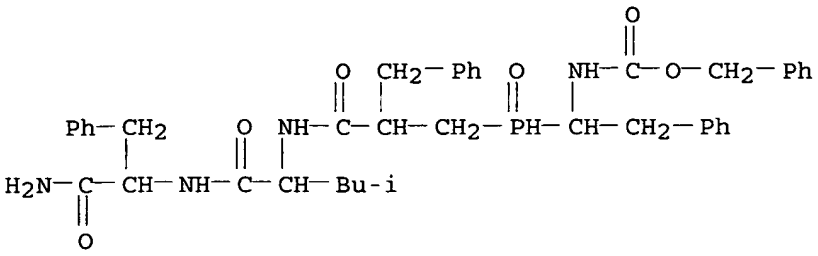
Absolute stereochemistry.



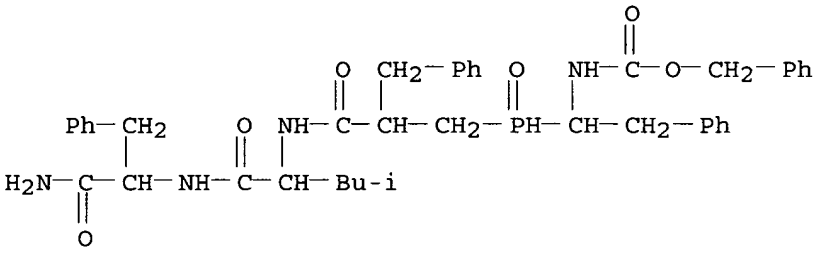
RN 126438-21-9 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-[[4-(phenylmethoxy)phenyl]methyl]hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



RN 126456-46-0 HCAPLUS
CN L-Phenylalaninamide, N-[1-oxo-2-(phenylmethyl)-3-[[2-phenyl-1-[[(phenylmethoxy)carbonyl]amino]ethyl]phosphinyl]propyl]-L-leucyl-, [2R-[2R*,3(1R*)]]- (9CI) (CA INDEX NAME)

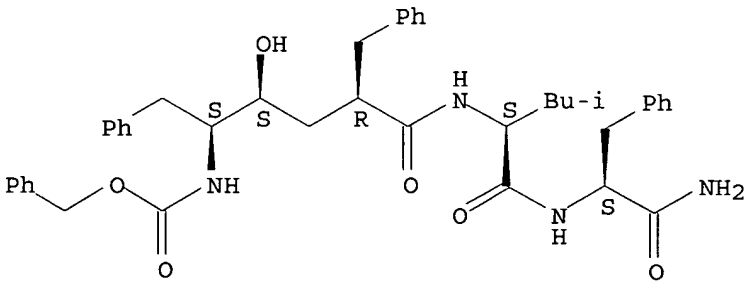


RN 126456-47-1 HCAPLUS
CN L-Phenylalaninamide, N-[1-oxo-2-(phenylmethyl)-3-[[2-phenyl-1-[[(phenylmethoxy)carbonyl]amino]ethyl]phosphinyl]propyl]-L-leucyl-, [2S-[2R*,3(1S*)]]- (9CI) (CA INDEX NAME)



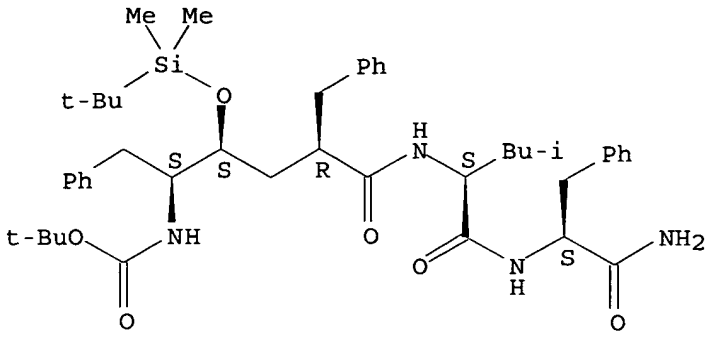
IT **126409-32-3P 126410-32-0P 126410-35-3P 126410-58-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for HIV protease inhibitor)
RN 126409-32-3 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-4-hydroxy-1-oxo-6-phenyl-5-[[(phenylmethoxy)carbonyl]amino]-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



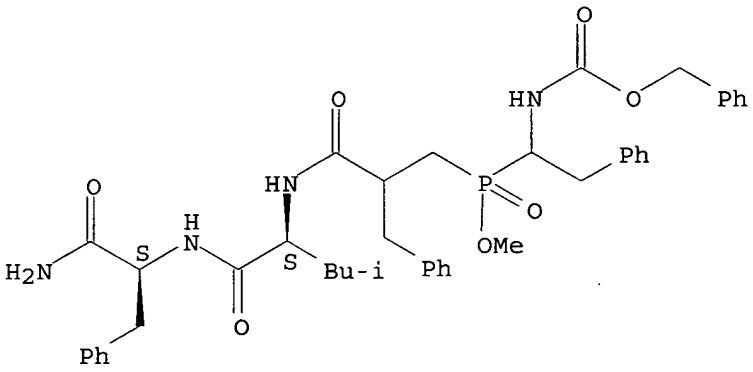
RN 126410-32-0 HCAPLUS
CN L-Phenylalaninamide, N-[(2R,4S,5S)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

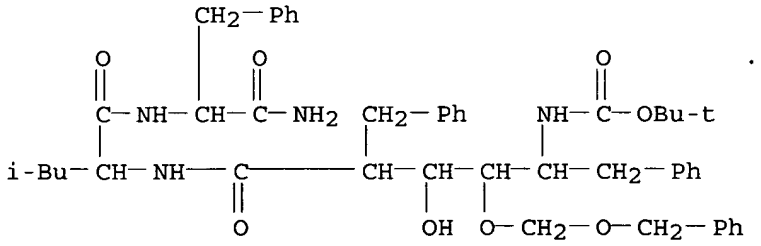


RN 126410-35-3 HCAPLUS
CN L-Phenylalaninamide, N-[2-[[methoxy[2-phenyl-1-[[(phenylmethoxy)carbonyl]amino]ethyl]phosphinyl]methyl]-1-oxo-3-phenylpropyl]-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 126410-58-0 HCAPLUS
CN L-Phenylalaninamide, N-[2,5,6-trideoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-phenyl-4-O-[(phenylmethoxy)methyl]-2-(phenylmethyl)-L-talonoyl]-L-leucyl- (9CI) (CA INDEX NAME)

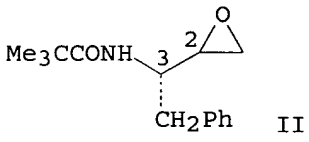


L5 ANSWER 31 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:576475 HCAPLUS
DOCUMENT NUMBER: 107:176475
TITLE: Peptide renin inhibitors
INVENTOR(S): Evans, Ben E.

PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 63 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 206090	A2	19861230	EP 1986-107870	19860610 <--
EP 206090	A3	19880427		
R: CH, DE, FR, GB, IT, LI, NL				
US 4665055	A	19870512	US 1985-745560	19850617 <--
JP 61293957	A2	19861224	JP 1986-139401	19860617 <--

PRIORITY APPLN. INFO.: US 1985-745560 A 19850617
OTHER SOURCE(S): CASREACT 107:176475
GI



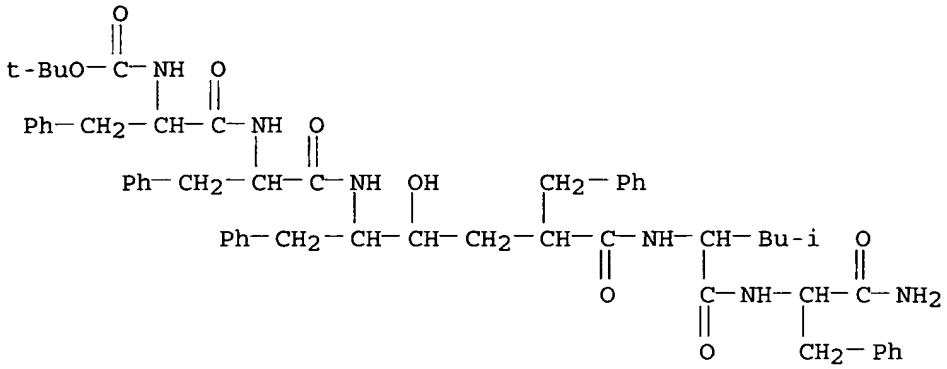
II

AB R1R2CHCH(OH)CH2CH(CH2R3)CONHCH(CH2R4)CH(OH)CH2COIVHCHR5R6[I; R1 = substituted NH2, substituted (di- or tri)amino acid amide residue and R2 = Me, alkylmethyl, (un)substituted PhCH2 or R1,R2 = H, linear (ar)alkyl or (ar)alkenyl; R3 = H, (hydroxy)alkyl, (un)substituted Ph; R4 = branched or linear alkyl, cycloalkyl, (un)substituted Ph; R5 = CHR7R8 (R7,R8 = H, alkyl, OH, Ph, cycloalkyl); R9 = CO2H, alkoxycarbonyl, (mono- and dialkyl) NH2, (un)substituted glycyl, (un)substituted amino acid residue, etc.], useful as renin inhibitors and for treatment of hypertension and hyperaldosteronism, were prepared Thus, condensation of H-Sta-Leu-NHCH2Ph.HCl [Sta = (3S,4S)-statyl] with (2RS, 4R, 5S)-PhCH2CH(NHCO2CMe3)CH(OSiMe2CMe3)CH2CH(CH2Ph)COR9 (III; R = OH), which was prepared in 8 steps from an oxirane II, in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide-HCl and 1-hydroxybenzotriazole gave, after desilylation, IV (R = Sta-Leu-NHCH2Ph).

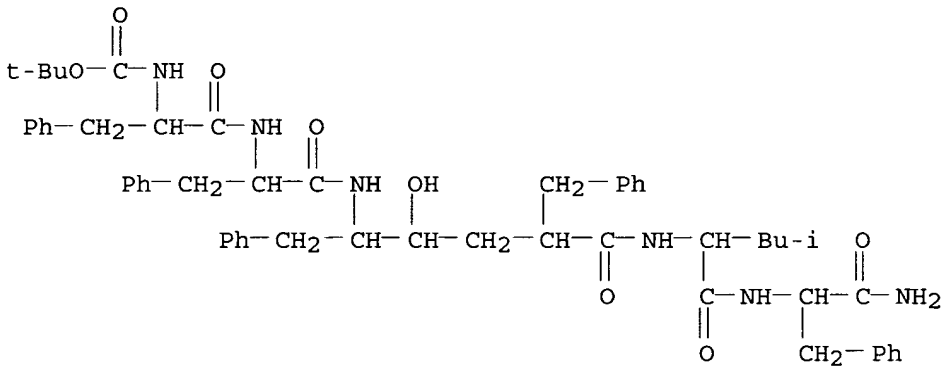
IT **98737-59-8P 98818-72-5P 98818-73-6P 98818-74-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as renin inhibitor and for treatment of hypertension and hyperaldosteronism)

RN 98737-59-8 HCAPLUS

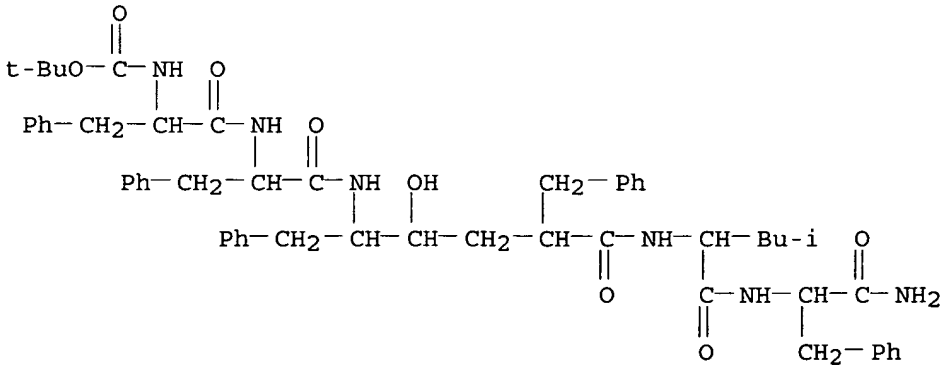
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4S*,5R*)]- (9CI) (CA INDEX NAME)



RN 98818-72-5 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4R*,5S*)]- (9CI) (CA INDEX NAME)

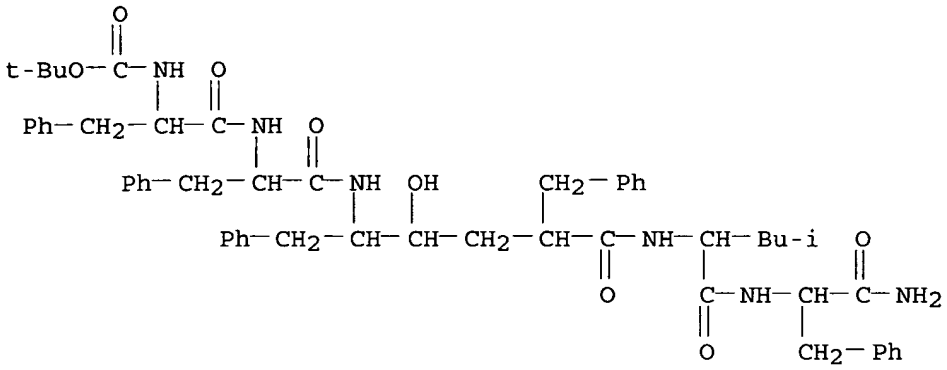


RN 98818-73-6 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4R*,5R*)]- (9CI) (CA INDEX NAME)

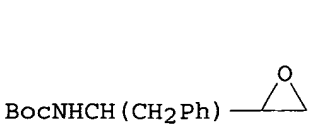


RN 98818-74-7 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-

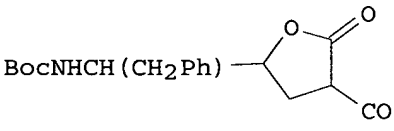
phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



L5 ANSWER 32 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:33459 HCAPLUS
DOCUMENT NUMBER: 106:33459
TITLE: Stereocontrolled synthesis of hydroxyethylene dipeptide isosteres using novel, chiral aminoalkyl epoxides; new renin inhibitor analogs
AUTHOR(S): Evans, Ben E.; Rittle, Kenneth E.; Ulm, Edgar H.; Veber, Daniel F.; Springer, James P.; Poe, Martin
CORPORATE SOURCE: Merck Sharp & Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Pept.: Struct. Funct., Proc. Am. Pept. Symp., 9th (**1985**), 743-6
CODEN: 54ZNAJ
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



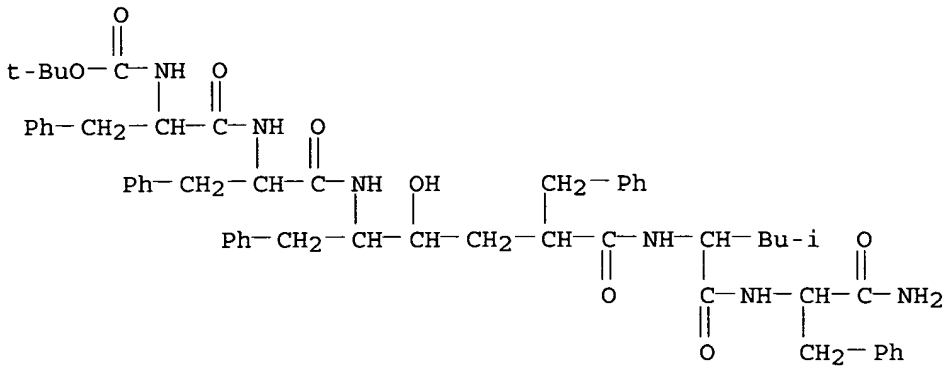
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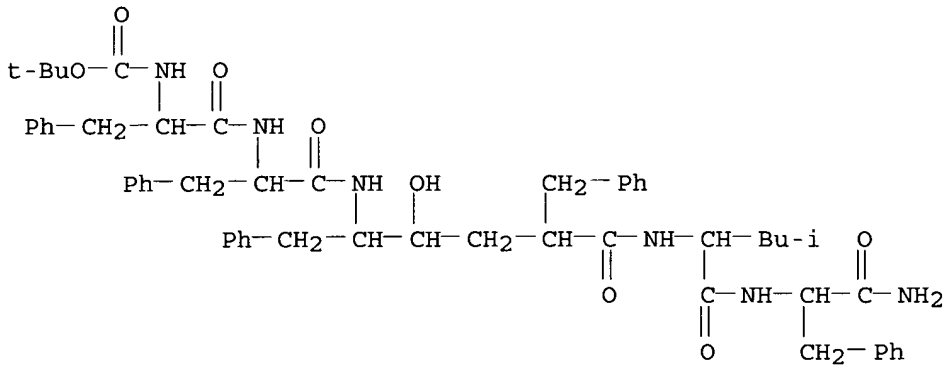
II

AB Renin inhibitor analogs Boc-Phe-Phe-X-Leu-Phe-NH2 (X = hydroxyethylene analog of Phe-Phe, Boc = Me3CO2C), Boc-X-Sta-Leu-NHCH2Ph [Sta = (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid residue], and Boc-X-ACHPA-Leu-NHCH2C6H4NH2-m [ACHPA = (3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid) were prepared from N-tert-butyoxycarbonyl-L-phenylalanine aldehyde via the oxirane I (chromatog. separable mixture of isomers) and the lactone II (pair of diastereomers).
IT **98737-59-8P 98818-72-5P 98818-73-6P 98818-74-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and renin inhibitory activity of)
RN 98737-59-8 HCAPLUS

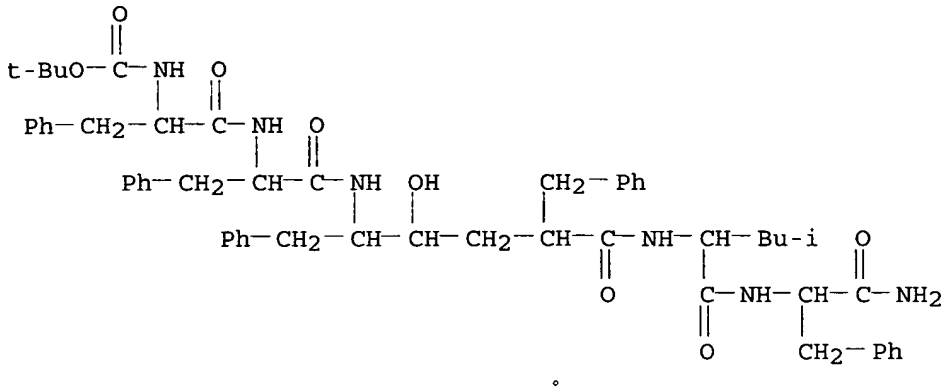
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4S*,5R*)]- (9CI) (CA INDEX NAME)



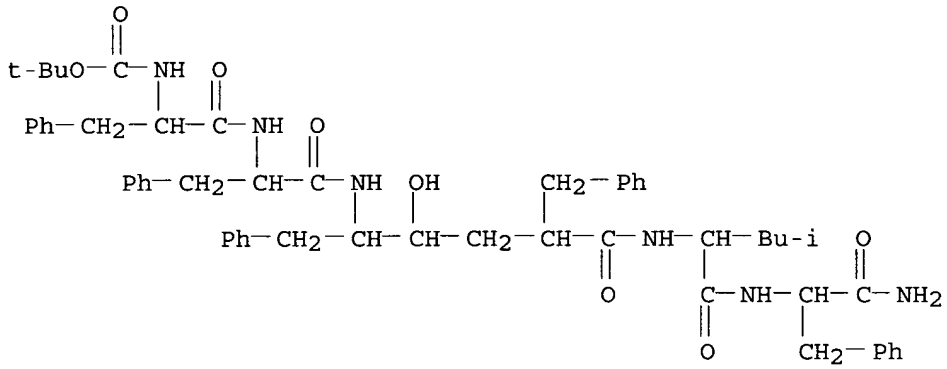
RN 98818-72-5 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4R*,5S*)]- (9CI) (CA INDEX NAME)



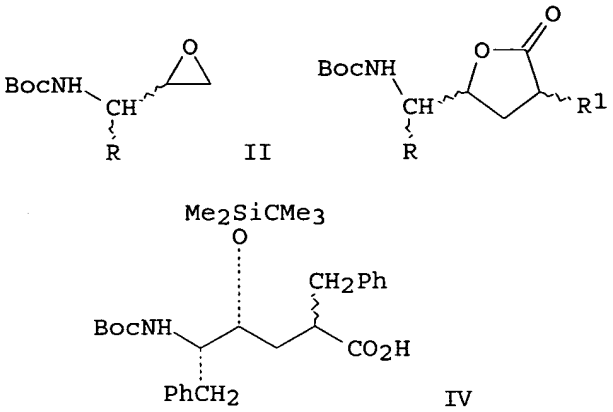
RN 98818-73-6 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4R*,5R*)]- (9CI) (CA INDEX NAME)



RN 98818-74-7 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



L5 ANSWER 33 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1985:596413 HCAPLUS
DOCUMENT NUMBER: 103:196413
TITLE: A stereocontrolled synthesis of hydroxyethylene dipeptide isosteres using novel, chiral aminoalkyl epoxides and γ-(aminoalkyl)-γ-lactones
AUTHOR(S): Evans, Ben E.; Rittle, Kenneth E.; Homnick, Carl F.; Springer, James P.; Hirshfield, Jordan; Veber, Daniel F.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Organic Chemistry (**1985**), 50(23), 4615-25
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 103:196413
GI

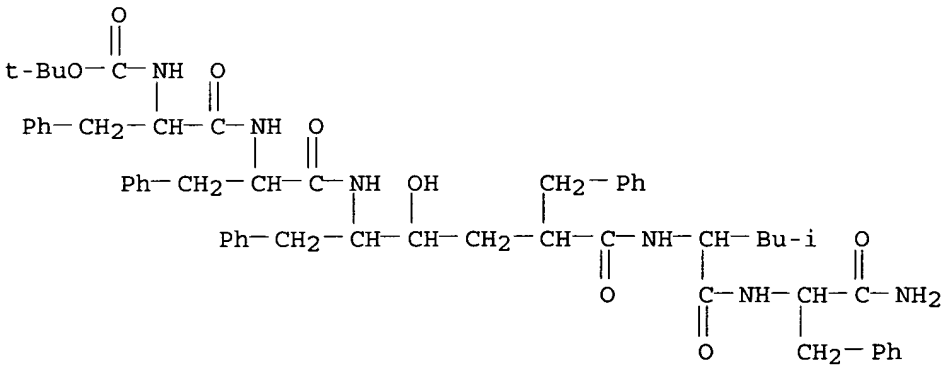


AB A stereocontrolled synthesis of the hydroxyethylene dipeptide isosteric unit NHCHRCH(OH)CH2CHR1CO (I) from chiral epoxides II (Boc = Me3CO2C) via γ-lactones III is described. The synthesis is capable of providing all 8 stereoisomers of I and is amenable to variations of R and R1. Thus, isosteric dipeptide IV was prepared and used in the synthesis of larger peptides. II (R = Ph) was prepared by the cycloaddn. of ylide CH2:SMe2 with aldehyde BocNHCH(CH2Ph)CHO.

IT **98737-59-8P 98818-72-5P 98818-73-6P**
98818-74-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

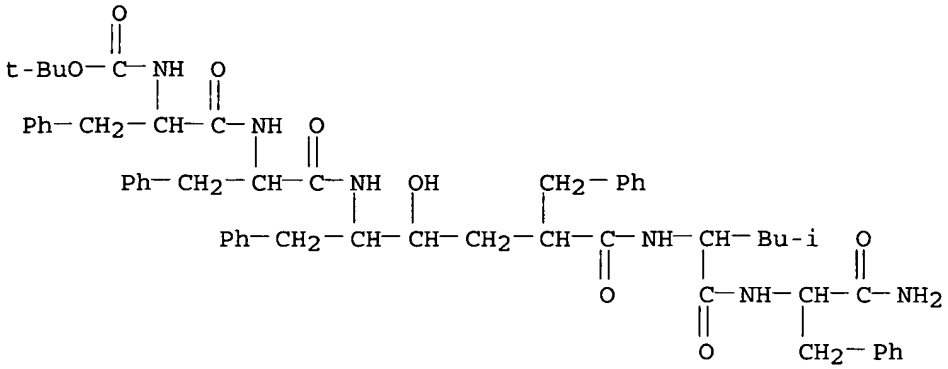
RN 98737-59-8 HCAPLUS

CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4S*,5R*)]- (9CI) (CA INDEX NAME)

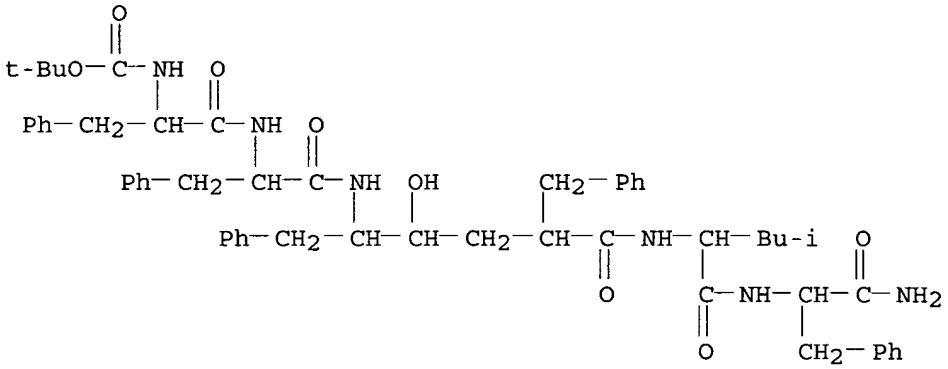


RN 98818-72-5 HCAPLUS

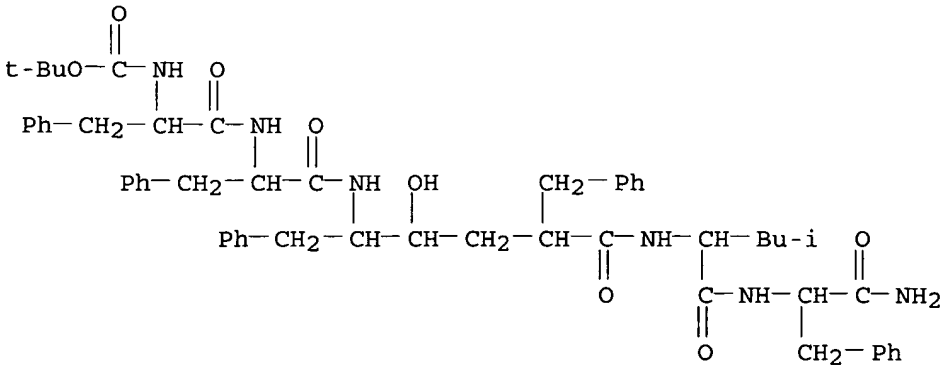
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4R*,5S*)]- (9CI) (CA INDEX NAME)



RN 98818-73-6 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2S-(2R*,4R*,5R*)]- (9CI) (CA INDEX NAME)



RN 98818-74-7 HCAPLUS
CN L-Phenylalaninamide, N-[5-[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-phenylalanyl]amino]-4-hydroxy-1-oxo-6-phenyl-2-(phenylmethyl)hexyl]-L-leucyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)



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FILE COVERS 1907 - 30 Nov 2004  VOL 141 ISS 23
FILE LAST UPDATED: 28 Nov 2004  (20041128/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que l9
L6  (      1715)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SECRETASE#/BI
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                ?TUMOUR? OR ?CANCER?)/BI AND L6
L8  (        31)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (SECRETASE(2A)INHIB?)/BI AND
                L7
L9           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (DRUG DELIVERY SYSTEMS+NT/CT
                OR (CARRIER OR FORM?)/BI) AND L8


=> b medl
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 FILE LAST UPDATED: 27 NOV 2004 (20041127/UP).  FILE COVERS 1950 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l17
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L11 (    116098)SEA FILE=MEDLINE ABB=ON  PLU=ON  PROTEASE INHIBITORS+NT/CT
L12 (     62748)SEA FILE=MEDLINE ABB=ON  PLU=ON  L11/MAJ
L13 (    185602)SEA FILE=MEDLINE ABB=ON  PLU=ON  L10(L)DT
L14 (    112602)SEA FILE=MEDLINE ABB=ON  PLU=ON  L13/MAJ
L15 (       317)SEA FILE=MEDLINE ABB=ON  PLU=ON  L14 AND L12
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L16 (         1)SEA FILE=MEDLINE ABB=ON  PLU=ON  SECRETASE# AND L15
L17           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  L16 AND PY<=2003


=> b embase
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 FILE COVERS 1974 TO 29 Nov 2004 (20041129/ED)

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 substance identification.

=> d que l24
L18 (       162)SEA FILE=EMBASE ABB=ON  PLU=ON  BETA SECRETASE INHIBITOR/CT OR
                GAMMA SECRETASE INHIBITOR/CT
L19 (       339)SEA FILE=EMBASE ABB=ON  PLU=ON  (SECRETASE(2A)INHIB?)/BI OR
                L18
L20 (     84632)SEA FILE=EMBASE ABB=ON  PLU=ON  "PROTEINASE INHIBITOR"+NT/CT
L21 (       299)SEA FILE=EMBASE ABB=ON  PLU=ON  ?SECRETASE? AND L20
L22 (       435)SEA FILE=EMBASE ABB=ON  PLU=ON  L19 OR L21
L23 (         7)SEA FILE=EMBASE ABB=ON  PLU=ON  ?NEOPLAS?/BI AND L22
L24           4 SEA FILE=EMBASE ABB=ON  PLU=ON  L23 AND PY<=2003


=> b biosis
FILE 'BIOSIS' ENTERED AT 09:27:41 ON 30 NOV 2004
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 24 November 2004 (20041124/ED)

FILE RELOADED: 19 October 2003.

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FILE LAST UPDATED:          25 NOV 2004      <20041125/UP>
MOST RECENT DERWENT UPDATE:     200476        <200476/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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    Derwent Chemistry Resource display fields  <<<

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PROCESSING COMPLETED FOR L9
PROCESSING COMPLETED FOR L28
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L29  ANSWER 1 OF 55  HCAPLUS  COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER:        2004:718305  HCAPLUS
DOCUMENT NUMBER:         141:236630
TITLE:                   Anti-angiogenic and anti-tumoral properties
                         of beta and gamma secretase
                         inhibitors
INVENTOR(S):             Paris, Daniel; Mullan, Michael J.
PATENT ASSIGNEE(S):      Roskamp Research LLC, USA
SOURCE:                  PCT Int. Appl., 44 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
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LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004073630	A2	20040902	WO 2004-US4494	20040218
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004229816	A1	20041118	US 2004-780905	20040218
PRIORITY APPLN. INFO.:			US 2003-319954P P	20030218

AB The present invention relates to methods of treating **tumors** or proliferative disorders that are associated with angiogenesis by administering g-**secretase** and b-**secretase** **inhibitors** that **inhibit** **secretases** involved in amyloid precursor protein processing. In particular, methods are provided to treat **tumors** or proliferative disorders, or to inhibit angiogenesis associated with **tumors**, proliferative or inflammatory disorders, in animals or humans in need of such treatment or angiogenic inhibition, by administering to the animal or human therapeutically effective amts. in unit dosage **form** of a composition containing a **carrier** and at least one g-**secretase** or b-**secretase** **inhibitor** that **inhibits** **secretase** APP processing.

IC ICM A61K
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
ST **antitumor** angiogenesis **inhibitor** beta gamma **secretase** **inhibitor** **cancer** therapy
IT Lung, **neoplasm**
(adenocarcinoma; antiangiogenic and **antitumor** effects of beta and gamma **secretase** **inhibitors**)
IT Angiogenesis inhibitors
Animal
Antitumor agents
Bladder, **neoplasm**
Eye, disease
Glaucoma (disease)
Head, **neoplasm**
Human
Kidney, **neoplasm**
Leukemia
Lymphoma
Mammary gland
Peptidomimetics
(antiangiogenic and **antitumor** effects of beta and gamma **secretase** **inhibitors**)
IT Amyloid precursor proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antiangiogenic and **antitumor** effects of beta and gamma

secretase inhibitors)
IT **Drug delivery systems**
(buccal; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(capsules; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Intestine, **neoplasm**
(colon; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Eye, disease
(diabetic retinopathy; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Hematopoiesis
(disorders; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(elixirs; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(emulsions; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Blood vessel
(endothelium; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Neuroglia, **neoplasm**
(glioblastoma; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(granules; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(inhalants; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Medical goods
(inhalers; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(injections, i.m.; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(injections, i.p.; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(injections, i.v.; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(injections, s.c.; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(intraocular, intraarterial, intracranial, intraventricular, intrasynovial, transepithelial, interstitial, atomizers and wafers; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(lozenges; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Eye, disease
(macula, degeneration; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)

IT Neck, anatomical
(**neoplasm**; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(ophthalmic; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(oral; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(parenterals; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Erythrocyte
(polycythemia; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(powders; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Disease, animal
(proliferative; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(rectal; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT Eye, disease
(retinitis pigmentosa; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(sachets; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(solns.; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(sprays; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(sublingual; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(suspensions; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(syrups; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(tablets; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(topical; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT **Drug delivery systems**
(transdermal; antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT 158736-49-3, β- **Secretase** 338454-52-7, γ-**Secretase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)
IT 62252-26-0, JLK 6 208255-51-0, DAPM 208255-80-5, DAPT 263563-09-3

Searched by P. Ruppel

292632-98-5, L-685458 314266-76-7, OM99-2 350228-37-4, P10-P4'StatV
552337-94-7, GL 189
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiangiogenic and **antitumor** effects of beta and gamma **secretase inhibitors**)

L29 ANSWER 3 OF 55 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:513522 HCAPLUS
DOCUMENT NUMBER: 141:71300
TITLE: A preparation of azabicycloalkane derivatives, useful as α7 nicotinic acetylcholine receptor (α7 nAChR) agonists
INVENTOR(S): Corbett, Jeffrey Wayne; Groppi, Vincent Edward, Jr.
PATENT ASSIGNEE(S): Upjohn Company, USA
SOURCE: PCT Int. Appl., 151 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004052348	A2	20040624	WO 2003-IB5525	20031128
WO 2004052348	A3	20041021		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-432527P P 20021211
OTHER SOURCE(S): MARPAT 141:71300
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to azabicycloalkane derivs. of **formula** azabicyclo-N(R1)-C(:X)-W [wherein: R1 is H, (cyclo)alkyl, or haloalkyl, etc.; X is O or S; W is a substituted benzene], useful as α7 nAChR agonists. Pharmacokinetics of the prepared compds. were evaluated (no biol. data). Blood-brain barrier penetration was investigated (no biol. data). For instance, chiral azabicycloheptane derivative I was prepared via addition of Me
3-bromopropargylate to N-Boc-pyrrole, reduction of the obtained azabicyclo[2.2.1]heptadiene II, hydrolysis of the obtained azabicycloheptane derivative III (R2 = OMe), reaction of the carboxylic acid III (R2 = OH) with diphenylphosphoryl azide and benzyl alc., resolution of the obtained exo-derivative IV, and hydrogenation.
IC ICM A61K031-00
CC 24-7 (Alicyclic Compounds)

Section cross-reference(s): 1, 63

IT Brain, **neoplasm**
(behavioral and cognitive problems, treatment of; preparation of azabicycloalkane derivs. useful as α7 nAChR agonists)

IT 9000-81-1, Acetylcholinesterase 158736-49-3, β- **Secretase** 338454-52-7, γ- **Secretase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**, drug component; preparation of azabicycloalkane derivs. useful as α7 nAChR agonists)

IT 272-23-1P, Thieno[2,3-b]pyridine 493-08-3P 704-91-6P, 1H-Indazole-6-carboxylic acid 1073-31-0P, 3,4-Thiophenedicarboxaldehyde 1074-76-6P, 2,4-Dimethyl-3-nitropyridine 1074-99-3P, 2,4-Dimethyl-5-nitropyridine 1851-22-5P, 3-Chloropyridine 1-oxide 5832-38-2P, 2-**Formyl**-4-methyl-5-nitropyridine 7040-07-5P, Furan-2,3-dicarboxaldehyde 7137-33-9P, Benzo[b]thiophene-2,3-dicarboxaldehyde 14757-78-9P, 3-Bromo-2-furaldehyde 15112-41-1P, 1,3-Benzoxazole-5-carboxylic acid 18853-32-2P, 3,4-Dicyanothiophene 21344-31-0P, Thieno[2,3-b]pyridine-5-carbonitrile 21472-88-8P, Ethyl 5-hydroxy-6-oxo-1,2,3,6-tetrahydropyridine-4-carboxylate 21473-14-3P 21473-16-5P, Exo-1-Azabicyclo[2.2.1]heptan-3-ol 21492-03-5P, Cis-4-(Hydroxymethyl)piperidin-3-ol 23680-40-2P, Methyl 3-bromopropiolate 24621-70-3P, 1H-Indol-2-ylmethanol 25557-50-0P, Thieno[2,3-b]pyridine-7-oxide 28872-85-7P, 2-(3-Bromo-2-furyl)-1,3-dioxolane 34668-25-2P, Ethyl furo[2,3-b]pyridine-2-carboxylate 34668-26-3P, Furo[2,3-b]pyridine-2-carboxylic acid 35350-37-9P 36404-88-3P, 2-Chloronicotinaldehyde 38180-46-0P, 3-Chloropyridine-2-carbonitrile 40789-79-5P, 2-(Benzoyloxy)-1-nitroethane 56538-57-9P, [[(Benzyloxy)carbonyl]amino](hydroxy)acetic acid 58123-77-6P, 3-Hydroxy-4-iodobenzoic acid 58237-86-8P, Methyl [[(benzyloxy)carbonyl]amino](methoxy)acetate 58621-52-6P, 1-(3,4-Dihydro-2H-chromen-6-yl)ethanone 59944-76-2P, Thieno[2,3-b]pyridine-2-carboxylic acid 60249-08-3P, Thieno[2,3-c]pyridine-5-carboxylic acid 60249-09-4P, Thieno[3,2-c]pyridine-6-carboxylic acid 65140-15-0P, 2-Aminothiophene hexachlorostannate 65898-38-6P, 5-Indancarboxylic acid 68867-17-4P, 1,3-Benzothiazole-5-carboxylic acid 72990-37-5P, 3-Chloroisonicotinaldehyde 74214-62-3P, Ethyl 9H-β-carboline-3-carboxylate 76429-73-7P, 2,3-Dihydrobenzofuran-5-carboxylic acid 86236-37-5P, Thieno[3,2-c]pyridine-2-carboxylic acid 86344-86-7P, Thieno[2,3-b]pyridine-6-carbonitrile 88568-95-0P 90322-32-0P, 2-Methyl-1,3-benzoxazole-5-carboxylic acid 90721-27-0P, Benzofuran-5-carboxylic acid 91486-39-4P, 4-(2-Chlorophenyl)-1H-pyrazole 94413-64-6P, Methyl 2-cyanoisonicotinate 94413-69-1P, Methyl 2-(aminomethyl)isonicotinate 103203-84-5P, Chromane-6-carboxylic acid 108763-47-9P, Methyl benzofuran-5-carboxylate 109274-83-1P, Ethyl 3-hydroxyfuro[2,3-b]pyridine-2-carboxylate 111042-90-1P, Methyl 3-aminothieno[3,2-b]pyridine-2-carboxylate 114077-82-6P, 4-Chloropyridine-3-carboxaldehyde 116538-95-5P, Thieno[3,2-b]pyridine-6-carbonitrile 117390-38-2P, Thieno[2,3-b]pyridine-5-carboxylic acid 117390-39-3P, Thieno[3,2-b]pyridine-6-carboxylic acid 119694-70-1P, 2-(1,3-Dioxolan-2-yl)-4-methyl-5-nitropyridine 123295-14-7P 129975-13-9P, Trans-4-Nitro-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester 130473-26-6P, 1H-Pyrrolo[2,3-c]pyridine-5-carboxaldehyde 130473-27-7P, 1H-Pyrrolo[2,3-c]pyridine-5-carboxylic acid 131489-60-6P, Ethyl E-4-(benzylamino)-2-butenoate 136117-69-6P, Methyl imidazo[1,2-a]pyridine-6-carboxylate 144017-84-5P, Trans-4-Amino-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester 153566-63-3P 154235-77-5P, 1,3-Benzoxazole-6-carboxylic acid 154650-88-1P, Methyl thieno[2,3-b]pyridine-2-carboxylate 157942-12-6P, Methyl 3-hydroxy-4-iodobenzoate 160893-70-9P, Methyl 2H-chromene-7-carboxylate

173340-19-7P 173724-95-3P 174676-79-0P 181873-33-6P 191150-86-4P, Benzyl cis-3-hydroxy-4-[(4-methylphenyl)sulfonyloxymethyl]piperidine-1-carboxylate 191150-87-5P, Benzyl cis-3-hydroxy-4-(hydroxymethyl)piperidine-1-carboxylate 197080-73-2P 206989-54-0P, tert-Butyl 4-(2-oxopropyl)piperidine-1-carboxylate 208519-38-4P, 2-Chloro-6-(hydroxymethyl)-4-[(trimethylsilyl)ethynyl]-3-pyridinol 208519-39-5P, [7-Chlorofuro[2,3-c]pyridin-5-yl]methanol 208519-40-8P, 7-Chlorofuro[2,3-c]pyridine-5-carboxaldehyde 208519-41-9P, 2-Chloro-6-(hydroxymethyl)-3-pyridinol 221128-29-6P 253332-81-9P, Methyl thieno[2,3-c]pyridine-5-carboxylate 280752-78-5P, 6-Bromo-2,3-dihydro-1,4-benzodioxin-2-yl)methanol 347187-30-8P, Thieno[3,2-b]pyridine-2-carboxylic acid 412023-64-4P, 2-(1,3-Dioxolan-2-yl)-3-furaldehyde 441044-90-2P, [7-Chloro-2-(trimethylsilyl)furo[2,3-c]pyridin-5-yl]methanol 473795-29-8P 473795-32-3P, Exo-3-(tert-Butoxycarbonylamino)-1-azabicyclo[2.2.1]heptane 473795-33-4P 473795-35-6P, endo-3-Azido-1-azabicyclo[2.2.1]heptane 473795-36-7P 473795-40-3P, tert-Butyl 4-(2-oxopropylidene)piperidine-1-carboxylate 473795-43-6P, tert-Butyl 4-(3-bromo-2-oxopropyl)piperidine-1-carboxylate 473795-46-9P, 1-Bromo-3-piperidin-4-ylacetone trifluoroacetate 478148-53-7P, 7-Chlorofuro[2,3-c]pyridine-5-carboxylic acid 478148-54-8P, 2,3-Dihydrofuro[2,3-c]pyridine-5-carboxylic acid 478148-59-3P, 5-Hydroxymethyl-2-trimethylsilylfuro[2,3-c]pyridine 478148-61-7P, Furo[2,3-c]pyridine-5-carboxaldehyde 478148-62-8P, Furo[2,3-c]pyridine-5-carboxylic acid 478148-64-0P, [6-Chloro-4-iodo-5-[(2-methyl-2-propenyl)oxy]-2-pyridinyl]methanol 478148-65-1P, [7-Chloro-3,3-dimethyl-2,3-dihydrofuro[2,3-c]pyridin-5-yl]methanol 478148-66-2P, [3,3-Dimethyl-2,3-dihydrofuro[2,3-c]pyridin-5-yl]methanol 478148-67-3P, 3,3-Dimethyl-2,3-dihydrofuro[2,3-c]pyridine-5-carboxaldehyde 478148-70-8P, (7-Chloro-2-methylfuro[2,3-c]pyridin-5-yl)methanol 478148-71-9P, (2-Methylfuro[2,3-c]pyridin-5-yl)methanol 478148-72-0P, 2-Methylfuro[2,3-c]pyridine-5-carboxaldehyde 478148-79-7P, Ethyl 3-[[(trifluoromethyl)sulfonyl]oxy]furo[2,3-b]pyridine-2-carboxylate 478148-81-1P, 3-(Allyloxy)-2-chloro-6-(hydroxymethyl)-4-iodopyridine 478148-82-2P, (7-Chloro-3-methyl-2,3-dihydrofuro[2,3-c]pyridin-5-yl)methanol 478148-83-3P, (3-Methyl-2,3-dihydrofuro[2,3-c]pyridin-5-yl)methanol 478148-84-4P, (3-Methyl-2,3-dihydrofuro[2,3-c]pyridin-5-yl)methyl acetate 478148-85-5P, (3-Methylfuro[2,3-c]pyridin-5-yl)methanol 478148-86-6P, 3-Methylfuro[2,3-c]pyridine-5-carboxaldehyde 478148-87-7P, 3-Methylfuro[2,3-c]pyridine-5-carboxylic acid 478148-89-9P, 3-Ethylfuro[2,3-c]pyridine-5-carboxylic acid 478148-91-3P, 3-Isopropylfuro[2,3-c]pyridine-5-carboxylic acid 478148-97-9P, Thieno[2,3-b]pyridine-6-carboxylic acid 478148-99-1P, Ethyl thieno[2,3-c]pyridine-2-carboxylate 478149-00-7P, Thieno[2,3-c]pyridine-2-carboxylic acid 478149-02-9P, Methyl thieno[3,2-b]pyridine-2-carboxylate 478149-05-2P, 3-Aminothiophene oxalate 478149-07-4P, Methyl thieno[3,2-c]pyridine-2-carboxylate 478149-12-1P, 5-(1,3-Dioxolan-2-yl)-1-methyl-1H-pyrrolo[2,3-c]pyridine 478149-13-2P, 1-Methylpyrrolo[2,3-c]pyridine-5-carboxaldehyde 478149-14-3P, 1-Methylpyrrolo[2,3-c]pyridine-5-carboxylic acid 478149-16-5P, Methyl benzothieno[3,2-c]pyridine-3-carboxylate 478149-21-2P, (3-Chlorofuro[2,3-c]pyridin-5-yl)methanol 478149-22-3P, 3-Chlorofuro[2,3-c]pyridine-5-carboxaldehyde 478149-23-4P, 3-Chlorofuro[2,3-c]pyridine-5-carboxylic acid 478149-25-6P, (3-Bromofuro[2,3-c]pyridin-5-yl)methanol 478149-26-7P, 3-Bromofuro[2,3-c]pyridine-5-carboxaldehyde 478149-27-8P, 3-Bromofuro[2,3-c]pyridine-5-carboxylic acid 478149-29-0P, Methyl furo[3,2-c]pyridine-6-carboxylate 478149-30-3P, Furo[3,2-c]pyridine-6-carboxylic acid 478149-49-4P, Methyl thieno[3,4-c]pyridine-6-carboxylate 478149-50-7P, Thieno[3,4-c]pyridine-6-carboxylic acid 478169-52-7P, 4-(Benzylamino)-2-chloro-6-(hydroxymethyl)-3-pyridinol 478169-54-9P,

4-Amino-5-hydroxypyridine-2-carboxylic acid 478169-65-2P, Methyl [1,3]-benzothiazole-5-carboxylate 478169-68-5P, Methyl 3-hydroxy-4-[(trimethylsilyl)ethynyl]benzoate 478169-69-6P, Methyl 4-acetyl-3-hydroxybenzoate 478169-70-9P 478169-71-0P, Methyl 3-methyl-1,2-benzisoxazole-6-carboxylate 478169-72-1P, 3-Methyl-1,2-benzisoxazole-6-carboxylic acid 500556-92-3P 508201-58-9P, 1-Azabicyclo[3.2.2]nonan-3-amine bis(4-methylbenzenesulfonate) 527680-65-5P, 2-Ethyl-7-iodo-2,3-dihydro-1,4-benzodioxine 527680-66-6P, 3-Ethyl-2,3-dihydro-1,4-benzodioxine-6-carbonitrile 527680-67-7P 527680-73-5P, 2-[(Benzyloxy)methyl]-6-bromo-2,3-dihydro-1,4-benzodioxine 527680-79-1P, 2-[(Benzyloxy)methyl]-7-bromo-2,3-dihydro-1,4-benzodioxine 527680-80-4P, 3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid 527681-05-6P, (2R)-7-Bromo-2-(phenoxymethyl)-2,3-dihydro-1,4-benzodioxine 527681-07-8P, (3R)-3-(Phenoxymethyl)-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid 527681-11-4P, Methyl 4,5-dihydroxypyridine-2-carboxylate 527681-12-5P, Methyl 2,3-dihydro-1,4-dioxino[2,3-c]pyridine-7-carboxylate 527681-13-6P, 2,3-Dihydro-1,4-dioxino[2,3-c]pyridine-7-carboxylic acid 527681-26-1P, Methyl 3-(allyloxy)-4-**formylbenzoate** 527681-29-4P, Methyl 3-(allyloxy)-4-vinylbenzoate 527681-33-0P, Chromane-7-carboxylic acid 527681-41-0P, Ethyl 4-(allyloxy)-3-vinylbenzoate 527681-42-1P, Ethyl 2H-chromene-6-carboxylate 527681-43-2P, 2H-Chromene-6-carboxylic acid 527681-47-6P, Methyl 4-hydroxy-3-vinylbenzoate 527681-48-7P, Methyl 3-**formyl**-4-[(1-methylprop-2-enyl)oxy]benzoate 527681-49-8P, Methyl 2-methyl-2H-chromene-6-carboxylate 527681-51-2P, 2-Methyl-2H-chromene-6-carboxylic acid 527681-56-7P, 2-Chloro-6-(hydroxymethyl)-4-vinylpyridin-3-ol 527681-57-8P, [5-(Allyloxy)-6-chloro-4-vinylpyridin-2-yl]methanol 527681-59-0P 527681-60-3P, 3,4-Dihydro-2H-pyrano[2,3-c]pyridin-6-ylmethanol 527681-62-5P, 3,4-Dihydro-2H-pyrano[2,3-c]pyridine-6-carboxylic acid 588702-80-1P, Methyl 2,3-dihydrobenzofuran-5-carboxylate 588720-10-9P, Ethyl 7-chloropyrrolo[1,2-c]pyrimidine-3-carboxylate 588720-11-0P, Ethyl 6-chloropyrrolo[1,2-c]pyrimidine-3-carboxylate 588720-12-1P, Ethyl 6-bromopyrrolo[1,2-c]pyrimidine-3-carboxylate 588720-13-2P, Pyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride 588720-14-3P, 7-Chloropyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride 588720-15-4P, 6-Chloropyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride 588720-16-5P, 6-Bromopyrrolo[1,2-c]pyrimidine-3-carboxylic acid hydrochloride 588720-29-0P, Imidazo[1,5-a]pyridine-7-carboxylic acid 588720-48-3P, Pyrrolo[1,2-a]pyrazine-3-carboxylic acid hydrochloride 588720-59-6P, Pyrazino[1,2-a]indole-3-carboxylic acid hydrochloride 655785-32-3P, Phenyl 4-iodo-1H-pyrazole-1-carboxylate 655785-40-3P, 4-Nitrophenyl 4-(2-chlorophenyl)-1H-pyrazole-1-carboxylate 711082-67-6P 711083-82-8P, (3S)-3-(Phenoxymethyl)-2,3-dihydro-1,4-benzodioxine-6-carboxylic acid 711084-61-6P, Oxazolo[4,5-c]pyridine-6-carboxylic acid 711084-89-8P 711085-20-0P 711085-34-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of azabicycloalkane derivs. useful as α7 nAChR agonists)

IT 89524-99-2P 130473-24-4P, 5-(1,3-Dioxolan-2-yl)-1H-pyrrolo[2,3-c]pyridine 153780-28-0P, Ethyl pyrrolo[1,2-a]pyrazine-3-carboxylate 208519-37-3P, 2-Chloro-6-(hydroxymethyl)-4-iodo-3-pyridinol 253332-82-0P, Methyl thieno[3,2-c]pyridine-6-carboxylate 478148-60-6P, Furo[2,3-c]pyridin-5-ylmethanol 478148-73-1P, 2-Methylfuro[2,3-c]pyridine-5-carboxylic acid 478149-20-1P, Furo[2,3-c]pyridin-5-ylmethyl acetate 500556-94-5P 500556-95-6P 508201-52-3P 527681-40-9P, Ethyl 4-(allyloxy)-3-**formylbenzoate**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(preparation of azabicycloalkane derivs. useful as α7 nAChR agonists)

IT 95-92-1, Diethyl oxalate 97-65-4, Itaconic acid, reactions 98-88-4, Benzoyl chloride 99-06-9, 3-Hydroxybenzoic acid, reactions 100-39-0, Benzyl bromide 100-46-9, Benzylamine, reactions 106-95-6, Allyl bromide, reactions 107-21-1, Ethylene glycol, reactions 108-47-4, 2,4-Lutidine 109-09-1, 2-Chloropyridine 109-94-4, Ethyl **formate** 144-62-7, Oxalic acid, reactions 149-73-5, Trimethyl orthoformate 254-04-6, 2H-Chromene 503-60-6, 1-Chloro-3-methyl-2-butene 563-96-2, Glyoxylic acid monohydrate 609-40-5, 2-Nitrothiophene 616-45-5, 2-Pyrrolidinone 621-84-1, Benzyl carbamate 623-50-7, Ethyl glycolate 625-48-9 626-60-8, 3-Chloropyridine 626-61-9, 4-Chloropyridine 922-67-8, Methyl propiolate 931-33-9, 4-Bromopyrrole-2-carboxaldehyde 932-41-2, 2,3-Thiophenedicarboxaldehyde 1003-29-8, Pyrrole-2-carboxaldehyde 1066-54-2, Trimethylsilylacetylene 1067-71-6, Diethyl(2-oxopropyl)phosphonate 1445-45-0, Trimethyl orthoacetate 1452-94-4, Ethyl 2-chloronicotinate 1458-98-6, 3-Bromo-2-methylpropene 1757-28-4, 5-Chloropyrrole-2-carboxaldehyde 2012-29-5, 2,4-Diiodophenol 2075-45-8, 4-Bromopyrazole 2258-42-6, Acetic **formic** anhydride 2365-48-2, Methyl thioglycolate 2374-03-0, 4-Amino-3-hydroxybenzoic acid 2458-12-0, 3-Amino-4-methylbenzoic acid 2627-86-3, (S)-(-)-α-Methylbenzylamine 2999-46-4, Ethyl isocyanoacetate 3141-26-2, 3,4-Dibromothiophene 3266-23-7, 2-Butene oxide 3469-69-0, 4-Iodopyrazole 3770-50-1, Ethyl indole-2-carboxylate 5176-27-2 6192-52-5, p-Toluenesulfonic acid monohydrate 6636-78-8, 2-Chloro-3-pyridinol 7342-82-7, 3-Bromothianaphthene 7379-35-3, 4-Chloropyridine hydrochloride 7677-24-9, Trimethylsilyl cyanide 7693-46-1, 4-Nitrophenyl chloroformate 13139-17-8, N-(Benzyloxycarbonyloxy)succinimide 13361-64-3, Propargyltrimethylsilane 14719-83-6, Methyl 4-chloro-3-nitrobenzoate 15905-18-7, Methyl nicotinate 1-oxide 22037-28-1, 3-Bromofuran 22288-78-4, Methyl 3-aminothiophene-2-carboxylate 24424-99-5, Di-tert-butyl dicarbonate 24589-98-8, Methyl 4-**formyl**-3-hydroxybenzoate 33515-58-1, 4-Chloropyrrole-2-carboxaldehyde 37746-78-4 43077-77-6, 4,5-Hydroxypyridine-2-carboxylic acid 79099-07-3, tert-Butyl 4-oxo-1-piperidinecarboxylate 82304-99-2, Ethyl 3-**formyl**-4-hydroxybenzoate 90843-31-5, 1-(2,3-Dihydrobenzofuran-5-yl)ethanone 107407-80-7, Ethyl pyrrolo[1,2-c]pyrimidine-3-carboxylate 107618-10-0, (6-Fluoro-2,3-dihydrobenzo-1,4-dioxin-2-yl)methanol 123536-14-1, (R)-(+)-3-Aminoquinuclidine dihydrochloride 145100-51-2, 2-[N,N-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine 187543-81-3 223389-15-9, n-Butyl furo[2,3-c]pyridine-5-carboxylate 280752-79-6, (7-Bromo-2,3-dihydro-1,4-benzodioxin-2-yl)methanol 473795-37-8, 1-Azabicyclo[3.2.1]octan-3-one hydrochloride 478148-95-7 527680-64-4, 1-(2,4-Diiodophenoxy)butan-2-ol 527681-03-4 655785-37-8, 2-(2-Chlorophenyl)malondialdehyde 711083-25-9 711085-16-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of azabicycloalkane derivs. useful as α7 nAChR agonists)

L29 ANSWER 5 OF 55 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-365423 [34] WPIX
DOC. NO. CPI: C2004-137964
TITLE: Screening compounds that modulates CD40L/CD40R signaling pathway, useful in treating nueronal inflammation or Alzheimer's disease, by contacting cells with a compound and CD40 ligand and measuring the level of a marker.
DERWENT CLASS: B04 D16
INVENTOR(S): MULLAN, M; TAN, J; TOWN, T C; MULLAN, M J
PATENT ASSIGNEE(S): (MULL-I) MULLAN M; (TANJ-I) TAN J; (TOWN-I) TOWN T C;

(UYSF-N) UNIV SOUTH FLORIDA
COUNTRY COUNT: 106
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004037204	A2	20040506	(200434)*	EN	76
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2004146949	A1	20040729	(200450)		
AU 2003284968	A1	20040513	(200468)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004037204	A2	WO 2003-US33971	20031027
US 2004146949	A1 Provisional	US 2002-421338P	20021025
		US 2003-694634	20031027
AU 2003284968	A1	AU 2003-284968	20031027

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003284968	A1 Based on	WO 2004037204

PRIORITY APPLN. INFO: US 2002-421338P 20021025; US 2003-694634 20031027
AN 2004-365423 [34] WPIX
AB WO2004037204 A UPAB: 20040527
NOVELTY - A research model for screening compounds suspected of modulating the CD40L/CD40R signaling pathway by interfering with the CD40L/CD40R signaling pathway in an animal, human, or system, comprises contacting a sample of cells with a compound and CD40 ligand and measuring the level or amount of a marker.

DETAILED DESCRIPTION - A research model for screening compounds suspected of modulating the CD40L/CD40R signaling pathway by interfering with the CD40L/CD40R signaling pathway in an animal, human, or system, comprises:

(a) contacting a first sample of cells with CD40 ligand and measuring the level or amount of a marker;

(b) contacting a second sample of cells with a compound and CD40 ligand and measuring the level or amount of a marker; and

(c) comparing the level or amount of the marker of the first sample of cells with the level or amount of the marker of the second sample of the cells.

INDEPENDENT CLAIMS are also included for:

(1) identifying compounds and/or small molecules that reduce, ameliorate, or modulate signs and/or symptoms associated with neuronal inflammation, brain injury, brain trauma, tauopathies or amyloidogenic diseases;

(2) treating nueronal inflammation, brain injury, brain trauma, tauopathies, amyloidogenic diseases or internal organ diseases related to amyloid plaque formation in an individual; and

(3) causing a desired biological effect in an animal, human or system afflicted with nueronal inflammation, brain injury, brain trauma, tauopathies or amyloidogenic diseases.

ACTIVITY - Neuroprotective; Nootropic; Cytostatic; Antidiabetic; Cerebroprotective. No biological data given.

MECHANISM OF ACTION - None Given.

USE - The method is useful in screening compounds suspected of modulating the CD40L/CD40R signaling pathway by interfering with the CD40L/CD40R signaling pathway in an animal, human or system. The methods, compounds and compositions are useful in treating nueronal inflammation, brain injury, brain trauma, tauopathies, amyloidogenic diseases or internal organ diseases related to amyloid plaque formation in an individual. The amyloidogenic diseases are Alzheimer's disease, scrapie, transmissible spongiform encelopathy, hereditary cerebral hemorrhage with amyloidosis Iceland-type, hereditary cerebral hemorrhage with amyloidosis Dutch-type, familial Mediterranean fever, familial amyloid nephropathy with urticaria and deafness (Muckle-Wells syndrome), myeloma or macroglobulinemia-associated idiopathy associated with amyloid, familial amyloid polyneuropathy (Portuguese), familial amyloid cardiomyopathy (Danish), systemic senile amyloidosis, familial amyloid polyneuropathy (Iowa), familial amyloidosis (Finnish), Gerstmann-Staussler-Scheinker syndrome, medullary carcinoma of thyroid, isolated atrial amyloid, Islets of Langerhans, diabetes Type II or insulinoma. Tauopathy are diseases like Alzheimer's disease, frontotemporal dementia, frontotemporal dementia with Parkinsonism, frontotemporal lobe dementia, pallipontonigral degeneration, progressive supranuclear palsy, multiple system tauopathy, multiple system tauopathy with presenile dementia, Wilhelmsen-Lynch disease, disinhibition-dementia-parkinsonism-amyotrophy complex, Pick's disease or Pick's disease-like dementia.

Dwg.0/9

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ACCESSION NUMBER: 2004:351986 BIOSIS
DOCUMENT NUMBER: PREV200400352628
TITLE: Notch Oncoproteins depend on gamma-secretase/presenilin activity for processing and function.
AUTHOR(S): Das, Indranil; Craig, Colleen; Funahashi, Yasuhiro; Jung, Kwang-Mook; Kim, Tae-Wan; Byers, Richard; Weng, Andrew P.; Kutok, Jeffery L.; Aster, Jon C.; Kitajewski, Jan [Reprint Author]
CORPORATE SOURCE: Dept Pathol and Obstet Gynecol, Columbia Univ Coll Phys and Surg, 630 W 168th St, New York, NY, 10032, USA jkk9@columbia.edu
SOURCE: Journal of Biological Chemistry, (July 16 2004) Vol. 279, No. 29, pp. 30771-30780, 30760. print. CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Aug 2004 Last Updated on STN: 26 Aug 2004

AB During normal development Notch receptor signaling is important in regulating numerous cell fate decisions. Mutations that truncate the extracellular domain of Notch receptors can cause aberrant signaling and promote unregulated cell growth. We have examined two types of truncated Notch oncoproteins that arise from proviral insertion into the Notch4 gene (Notch4/int-3) or a chromosomal translocation involving the Notch1 gene (TAN-1). Both Notch4/int-3 and TAN-1 oncoproteins lack most or all of their ectodomain. Normal Notch signaling requires gamma-secretase/presenilin-mediated proteolytic processing, but whether Notch

oncoproteins are also dependent on gamma-secretase/presenilin activity is not known. We demonstrate that Notch4/int-3-induced activation of the downstream transcription factor, CSL, is abrogated in cells deficient in presenilins or treated with a pharmacological **inhibitor** of gamma-**secretase**/presenilins. Furthermore, we find that both Notch4/int-3 and TAN-1 accumulate at the cell surface, where presenilin-dependent cleavage occurs, when gamma-secretase/presenilin activity is **inhibited.** gamma-**Secretase**/presenilin **inhibition** effectively blocks cellular responses to Notch4/int-3, but not TAN-1, apparently because some TAN-1 polypeptides lack transmembrane domains and do not require gamma-secretase/presenilin activity for nuclear access. These studies highlight potential uses and limitations of gamma-**secretase**/presenilin **inhibitors** in targeted therapy of Notch-related **neoplasms.**

CC Enzymes - General and comparative studies: coenzymes 10802
Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); **Tumor** Biology
IT Chemicals & Biochemicals
CSL: transcription factor; Notch oncoproteins; Notch receptor; TAN-1 polypeptides; gamma-**secretase**: **inhibition**; presenilin: inhibition
IT Miscellaneous Descriptors
proteolytic processing
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HUVEC cell line (cell line): human umbilical vein endothelial cells
HeLa cell line (cell line): human cervical carcinoma cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
MEF cell line (cell line): mouse embryo fibroblast cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 338454-52-7 (gamma-secretase)
GEN human Notch4 gene (Hominidae); human TAN-1 gene (Hominidae)

L29 ANSWER 9 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:334198 BIOSIS
DOCUMENT NUMBER: PREV200400331407
TITLE: Partial loss of presenilins causes seborrheic keratosis and autoimmune disease in mice.
AUTHOR(S): Tournoy, Jos; Bossuyt, Xavier; Snellinx, An; Regent, Marleen; Garmyn, Marian; Serneels, Lutgarde; Saftig, Paul; Craessaerts, Katleen; De Strooper, Bart; Hartmann, Dieter [Reprint Author]
CORPORATE SOURCE: Ctr Human Genet CB 4Neuronal Cell Biol Lab, Catholic Univ Louvain, Herestr 49, B-3000, Louvain, Belgium dieter.hartmann@med.kuleuven.ac.be
SOURCE: Human Molecular Genetics, (July 1 2004) Vol. 13, No. 13,

pp. 1321-1331. print.
ISSN: 0964-6906 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Aug 2004
Last Updated on STN: 4 Aug 2004

AB Presenilin (PS1) and (PS2) are the centers of gamma-secretase that release Abeta from APP in Alzheimer's disease (AD). They cleave signaling proteins like Notch and downregulate beta-catenin to modulate Wnt signaling. Inactivation of PS1 or PS1 and PS2 causes a prenatally lethal 'Notch phenotype,' which has hampered investigation of PS function in adulthood seriously. We have thus turned towards PS1+/-PS2-/- mice which carry the most severe reduction of PS alleles compatible with survival, to analyze the consequences of impaired PS function especially in adulthood. In these 'partial deficient' mice, PS1 protein concentration is considerably lowered, functionally reflected by reduced gamma-secretase activity and impaired beta-catenin downregulation. Their phenotype is normal up to apprx6 months, when the majority of the mice develop an autoimmune disease characterized by dermatitis, glomerulonephritis, keratitis and vasculitis, as seen in human systemic lupus erythematosus. Besides B-cell dominated infiltrates, we observe a hypergammaglobulinemia with immune complex deposits in several tissues, high-titer nuclear autoantibodies and an increased CD4+/CD8+ ratio. The mice further develop a benign skin hyperplasia similar to human seborrheic keratosis as opposed to malignant keratocarcinomata observed in skin-specific PS1 'full' knockouts. A partial reduction of PS function in PS1+/-PS2-/- mice causes a novel phenotype in adulthood unrelated to the developmental defects of full knockouts. As PS1+/-PS2+/- mice remain healthy, this points towards a sharply defined minimum of PS function. Skin and immune system appear to be especially sensitive targets of impaired PS function and may need careful monitoring if gamma-**secretase inhibitors** are envisaged for treating AD.

CC Cytology - Animal 02506
Genetics - General 03502
Genetics - Animal 03506
Cardiovascular system - Blood vessel pathology 14508
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Urinary system - Pathology 15506
Bones, joints, fasciae, connective and adipose tissue - Pathology 18006
Integumentary system - Physiology and biochemistry 18504
Integumentary system - Pathology 18506
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
Allergy 35500

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Integumentary System (Chemical Coordination and Homeostasis); Molecular Genetics (Biochemistry and Molecular Biophysics)

IT Parts, Structures, & Systems of Organisms
B-cells: blood and lymphatics, immune system; immune system: immune system; skin: integumentary system

IT Diseases
autoimmune disease: immune system disease, genetics
Autoimmune Diseases (MeSH)

IT Diseases
dermatitis: integumentary system disease
Dermatitis (MeSH)

IT Diseases
glomerulonephritis: urologic disease
Glomerulonephritis (MeSH)
IT Diseases
hypergammaglobulinemia: blood and lymphatic disease, immune system disease
Hypergammaglobulinemia (MeSH)
IT Diseases
malignant keratocarcinomata: integumentary system disease, **neoplastic** disease
IT Diseases
seborrheic keratosis: integumentary system disease, genetics
Keratosis, Seborrheic (MeSH)
IT Diseases
systemic lupus erythematosus: connective tissue disease, immune system disease
Lupus Erythematosus, Systemic (MeSH)
IT Diseases
vasculitis: vascular disease
Vasculitis (MeSH)
IT Chemicals & Biochemicals
PS1: inactivation; PS2: inactivation; beta-catenin: downregulation; gamma-secretase; high-titer nuclear autoantibodies; immune complex deposits; presenilins: partial loss
IT Miscellaneous Descriptors
CD4-positive/CD8-positive ratio; Wnt signaling
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 338454-52-7 (gamma-secretase)

L29 ANSWER 11 OF 55 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:783187 HCAPLUS
DOCUMENT NUMBER: 141:364052
TITLE: Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells
AUTHOR(S): Dontu, Gabriela; Jackson, Kyle W.; McNicholas, Erin; Kawamura, Mari J.; Abdallah, Wissam M.; Wicha, Max S.
CORPORATE SOURCE: Comprehensive Cancer Center, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
SOURCE: Breast Cancer Research (2004), 6(6), R605-R615
CODEN: BRCRFS; ISSN: 1465-542X
URL: http://breast-cancer-research.com/content/pdf/bcr920.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Introduction Notch signaling has been implicated in the regulation of cell-fate decisions such as self-renewal of adult stem cells and differentiation of progenitor cells along a particular lineage. Moreover, depending on the cellular and developmental context, the Notch pathway acts as a regulator of cell survival and cell proliferation. Abnormal expression of Notch receptors has been found in different types of epithelial metaplastic lesions and **neoplastic** lesions,

suggesting that Notch may act as a proto-oncogene. The vertebrate Notch 1 and Notch4 homologs are involved in normal development of the mammary gland, and mutated **forms** of these genes are associated with development of mouse mammary **tumors.** In order to determine the role of Notch signaling in mammary cell-fate determination, we have utilized a newly described in vitro system in which mammary stem/progenitor cells can be cultured in suspension as nonadherent 'mammospheres'. Notch signaling was activated using exogenous ligands, or was inhibited using previously characterized Notch signaling antagonists. Results Utilizing this system, we demonstrate that Notch signaling can act on mammary stem cells to promote self-renewal and on early progenitor cells to promote their proliferation, as demonstrated by a 10-fold increase in secondary mammosphere **formation** upon addition of a Notch-activating DSL peptide. In addition to acting on stem cells, Notch signaling is also able to act on multipotent progenitor cells, facilitating myoepithelial lineage-specific commitment and proliferation. Stimulation of this pathway also promotes branching morphogenesis in three-dimensional Matrigel cultures. These effects are completely inhibited by a Notch4 blocking antibody or a gamma **secretase inhibitor** that blocks Notch processing. In contrast to the effects of Notch signaling on mammary stem/progenitor cells, modulation of this pathway has no discernnable effect on fully committed, differentiated, mammary epithelial cells. These studies suggest that Notch signaling plays a critical role in normal human mammary development by acting on both stem cells and progenitor cells, affecting self-renewal and lineage-specific differentiation. Based on these findings we propose that abnormal Notch signaling may contribute to mammary carcinogenesis by deregulating the self-renewal of normal mammary stem cells.

CC 14-1 (Mammalian Pathological Biochemistry)

IT Cell proliferation
Human
Mammary gland, **neoplasm**
Signal transduction, biological
Transformation, **neoplastic**
(role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 13 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:288953 BIOSIS
DOCUMENT NUMBER: PREV200400287710
TITLE: Opposing roles for Notch1 and Notch2 in Medulloblastomas.
AUTHOR(S): Eberhart, Charles [Reprint Author]; Mikolaenko, Irina; Ball, Douglas; Perry, Arie; Fan, Xing
CORPORATE SOURCE: Pathology, Johns Hopkins University, 720 Rutland Ave - Ross Bldg 558, Baltimore, MD, 21205, USA
ceberha@jhmi.edu
SOURCE: FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 386.6.
http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004

AB Notch signalling plays an important role in both cell fate decisions and stem cell maintenance and proliferation. Here, in human fetal cerebellum, we demonstrate that the Notch2 receptor is predominantly expressed in proliferating progenitors, while Notch1 is detected in post-mitotic differentiating cells. Expression of truncated, constitutively active Notch1 or Notch2 in embryonal brain **tumour** cell lines caused opposing effects consistent with this expression pattern, with proliferation, cell number increase, soft agar colony formation and xenograft growth inhibited by Notch1 and promoted by Notch2. Given the oncogenic effects of Notch2, we analyzed its gene dosage in 39 embryonal brain **tumours**, detecting amplification in 10% of cases. In addition, increased Notch activity in medulloblastomas, as evidenced by Hes1 protein expression, was associated with significantly shorter patient survival (P = 0.01). **Inhibition** of gamma-**secretase** activity, which prevents activation of Notch, arrested **tumour** growth in vitro and may be useful therapeutically. Our data indicate that Notch1 and Notch2 can have opposing effects on **tumorigenesis**, and establish Notch2 as an oncogene amplified in human **tumours**.
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CC General biology - Symposia, transactions and proceedings 00520
Genetics - General 03502
Genetics - Human 03508
Nervous system - Pathology 20506
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Neurology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences)

IT Diseases
medulloblastoma: **neoplastic** disease, nervous system disease
Medulloblastoma (MeSH)

IT Chemicals & Biochemicals
Hes1: expression; Notch1; Notch2; gamma-**secretase**: **inhibition**

IT Miscellaneous Descriptors
survival

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 338454-52-7 (gamma-secretase)

GEN human Notch2 gene (Hominidae): oncogene

L29 ANSWER 15 OF 55 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-636701 [60] WPIX
DOC. NO. CPI: C2003-174092
TITLE: New peptides and proteins, useful for treating wounds and arteriosclerosis, and screening of **angiogenesis** inhibitors, contain the basic amino acid cluster region of beta-1,6-N-acetylglucosaminyltransferase.
DERWENT CLASS: B04 D16
INVENTOR(S): MIYOSHI, E; SAITO, T; TANIGUCHI, N
PATENT ASSIGNEE(S): (SUNR) SUNTORY LTD
COUNTRY COUNT: 33
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003060131	A1	20030724	(200360)*	JA	68
RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SI SK TR					
W: AU BR CA CN IL JP KR US					
AU 2002362185	A1	20030730	(200421)		
EP 1460134	A1	20040922	(200462)	EN	
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SI SK TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003060131	A1	WO 2002-JP13879	20021227
AU 2002362185	A1	AU 2002-362185	20021227
EP 1460134	A1	EP 2002-792072	20021227
		WO 2002-JP13879	20021227

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002362185	A1 Based on	WO 2003060131
EP 1460134	A1 Based on	WO 2003060131

PRIORITY APPLN. INFO: JP 2002-2056 20020109

AN 2003-636701 [60] WPIX

AB WO2003060131 A UPAB: 20030919

NOVELTY - Peptides and proteins (I), which promote **angiogenesis** and contain the basic amino acid cluster region of beta -1,6-N-acetylglucosaminyltransferase (GnT-V), are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) **angiogenesis** agents containing (I);

(2) a method for screening potential **angiogenesis** inhibitors, using (I) or cells expressing (I);

(3) a method for screening potential **angiogenesis** inhibitors, using secreted GnT-V released from its anchorage to Golgi bodies by addition of a protease such as beta -secretase or gamma -secretase;

(4) compounds (II) identified by these screening methods;

(5) antibodies recognizing (I);

(6) a method for the assay of (I) using these antibodies.

ACTIVITY - Vulnerary; Antiarteriosclerotic; Cytostatic; **Angiogenic**; Antiangiogenic.

Induction of **angiogenesis** in human umbilical vein epithelial cells (HUVAC) is measured by capillary tube formation assay (Ashoton, J.Biol.Chem.1999 (274) 35562-35570) and migration assay (Zeng, J.Biol.Chem.2001 (276) 3271-3279). Induction of **angiogenesis** by GnT-V Delta 73 (74-741 of GnT-V) is similar to that by whole GnT-V, while GnT-V Delta 436 (437-741 of GnT-V) (which does not contain the basic amino acid cluster region 254-269) does not induce **angiogenesis.**

MECHANISM OF ACTION - None given.

USE - (I) are **angiogenesis** promoters useful as vulneraries in the treatment and prevention of arteriosclerosis, and wound healing. Inhibitors of **angiogenesis** identified by screening using (I) are useful in the treatment and prevention of **angiogenesis**-related diseases such as cancer.

Dwg.0/7

L29 ANSWER 17 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:466447 BIOSIS
DOCUMENT NUMBER: PREV200300466447
TITLE: Presenilin-dependent "gamma-secretase" processing of deleted in colorectal **cancer** (DCC).
AUTHOR(S): Taniguchi, Yoshihito; Kim, Seong-Hun; Sisodia, Sangram S. [Reprint Author]
CORPORATE SOURCE: Dept. of Neurobiology, Pharmacology, and Physiology, University of Chicago, 947 East 58th St., MC0926, Chicago, IL, 60637, USA
ssisodia@drugs.bsd.uchicago.edu
SOURCE: Journal of Biological Chemistry, (August 15 2003) Vol. 278, No. 33, pp. 30425-30428. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 2003
Last Updated on STN: 8 Oct 2003

AB The presenilin-gamma-secretase complex plays a critical role in mediating intramembranous proteolysis of several type I membrane proteins, including beta-amyloid precursor protein (APP) and Notch. We now show that deleted in colorectal **cancer** (DCC) is subject to proteolysis within the ectodomain segment both in cultured cells and in vivo and that the residual membrane-tethered DCC "stub" is subsequently processed by gamma-secretase to generate a derivative termed DCC-intracellular domain (ICD). The production of DCC-ICD is inhibited by selective gamma-**secretase inhibitors**, and by the expression of the dominant negative PS1 D385A variant. Moreover, the membrane-tethered DCC "stubs" accumulate to high levels in PS1-deficient embryos. We also demonstrate that expression of a DCC-Gal4 chimera is capable of activating transcription in a luciferase-based reporter assay and this activity is dependent on gamma-secretase activity. Our findings offer the proposal that DCC performs dual roles both as a cell surface receptor that modulates intracellular signaling pathways and as a transcriptional coactivator that relies on gamma-secretase-dependent production and nuclear translocation of the cytoplasmic domain.

CC Cytology - General 02502
Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Digestive system - Pathology 14006
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; **Tumor** Biology

IT Diseases
colorectal **cancer**: digestive system disease, **neoplastic** disease
Colorectal **Neoplasms** (MeSH)

IT Chemicals & Biochemicals
Notch: protein; beta-amyloid precursor protein; gamma-secretase; presenilin; presenilin-gamma-secretase complex

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HEK293 cell line (cell line): human embryonic kidney cells

Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 338454-52-7 (gamma-secretase)

L29 ANSWER 19 OF 55 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003453016 EMBASE
TITLE: Notch signaling as a therapeutic target in cancer: A new approach to the development of cell fate modifying agents.
AUTHOR: Nickoloff B.J.; Osborne B.A.; Miele L.
CORPORATE SOURCE: L. Miele, Dept. of Biopharmaceutical Sciences, Cancer Center, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612, United States. lmiele@uic.edu
SOURCE: Oncogene, (2 Oct 2003) 22/43 (6598-6608).
Refs: 137
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Notch signaling controls cell fate decisions including during development and stem cell renewal and differentiation in many postnatal tissues. Increasing evidence suggests that the Notch signaling network is frequently deregulated in human malignancies and that genetic or pharmacological manipulation of Notch signaling is a novel potential strategy for the treatment of human **neoplasms.** This review article summarizes the most recent preclinical and clinical evidence linking Notch signaling to cancer, delineates questions that remain unanswered and explores potential biopharmacological strategies to manipulate Notch signaling in vivo.
CT Medical Descriptors:
*signal transduction
cell fate
stem cell
cell renewal
cell differentiation
cancer
drug effect
drug efficacy
antineoplastic activity
leukemia
protein function
human
nonhuman
review
priority journal
Drug Descriptors:
*protein Notch
***antineoplastic agent: DV, drug development**
receptor blocking agent: DV, drug development
gamma secretase
enzyme inhibitor: DV, drug development
tumor necrosis factor alpha converting enzyme inhibitor: DV, drug development
fucosyltransferase
glycosyltransferase inhibitor: DV, drug development
oligopeptide: DV, drug development
RN (fucosyltransferase) 56626-18-7

L29 ANSWER 21 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:164462 BIOSIS
DOCUMENT NUMBER: PREV200300164462
TITLE: Glycoprotein 130 signaling regulates Notch1 expression and activation in the self-renewal of mammalian forebrain neural stem cells.
AUTHOR(S): Chojnacki, Andrew; Shimazaki, Takuya; Gregg, Christopher; Weinmaster, Gerry; Weiss, Samuel [Reprint Author]
CORPORATE SOURCE: Genes and Development Research Group, Department of Cell Biology and Anatomy, Faculty of Medicine, University of Calgary, Calgary, Alberta, T2N 4N1, Canada
weiss@ucalgary.ca
SOURCE: Journal of Neuroscience, (March 1 2003) Vol. 23, No. 5, pp. 1730-1741. print.
ISSN: 0270-6474 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 2003
Last Updated on STN: 2 Apr 2003

AB Glycoprotein 130 (gp130) and Notch signaling are thought to participate in neural stem cell (NSC) self-renewal. We asked whether gp130 regulates Notch activity in forebrain epidermal growth factor (EGF)-responsive NSCs. Disruption of Notch1 using antisense or a gamma-**secretase inhibitor** demonstrated a requirement for Notch1 in the maintenance and proliferation of NSCs. Ciliary neurotrophic factor (CNTF) activation of gp130 in NSCs rapidly increased Notch1 expression. NOTCH1 activation, indicated by **tumor** necrosis factor alpha-converting enzyme (TACE)- and presenilin-mediated processing, also increased. Infusion of EGF+CNTF into adult forebrain lateral ventricles increased periventricular NOTCH1 compared with EGF alone. Neither Hes1 (hairy and enhancer of split) nor Hes5 appeared to mediate gp130-enhanced NOTCH1 signaling that regulates NSC maintenance. This is the first example of a link between gp130 signaling and NOTCH1 in regulating NSC self-renewal.

CC Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Nervous system - Physiology and biochemistry 20504

IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)

IT Parts, Structures, & Systems of Organisms
forebrain: nervous system; forebrain neural stem cells: nervous system, self-renewal; lateral ventricles: nervous system

IT Chemicals & Biochemicals
Hes1: hairy and enhancer of split; Hes5: hairy and enhancer of split; Notch: activity, signaling; Notch1: expression; antisense inhibitor; ciliary neurotrophic factor [CNTF]: activation; epidermal growth factor; gamma-**secretase inhibitor**; glycoprotein 130 [gp130]: signaling; **tumor** necrosis factor-alpha-converting enzyme [TACE]

IT Miscellaneous Descriptors
presenilin-mediated processing

ORGN Classifier
Mammalia 85700
Super Taxa
Vertebrata; Chordata; Animalia
Organism Name
mammal (common)
Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 62229-50-9 (epidermal growth factor)
42013-48-9 (glycoprotein 130)
42013-48-9 (gp130)
151769-16-3 (**tumor** necrosis factor-alpha-converting enzyme)
151769-16-3 (TACE)

L29 ANSWER 23 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:165875 BIOSIS
DOCUMENT NUMBER: PREV200400161099
TITLE: Activated Notch signaling might be a novel therapeutic target for multiple myeloma.
AUTHOR(S): Jundt, Franziska [Reprint Author]; Proebsting, Kristina Schulze [Reprint Author]; Anagnostopoulos, Ioannis; Mathas, Stephan [Reprint Author]; Stein, Harald; Doerken, Bernd [Reprint Author]
CORPORATE SOURCE: Hematology, Oncology and Tumorimmunology, Max-Delbrueck-Center for Molecular Medicine, Humboldt University, Charite, Berlin, Germany
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 928a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004
AB Notch signaling plays a key role in the development and differentiation of various hematopoietic lineages. In the hematopoietic system, Notch receptors are expressed in early hematopoietic stem cells, whereas Notch ligands are found in bone marrow stroma, which provides the microenvironment necessary for stem cell survival and differentiation. In addition, we recently demonstrated that Notch signaling is involved in the pathogenesis of B-cell-derived **tumor** cells of Hodgkin lymphoma (Blood. 2002;99:3398-3403). We described a novel mechanism for the oncogenic capacity of Notch by showing that interactions of overexpressed intact Notch1 and Notch2 receptors on **tumor** cells with their cognate ligand Jagged1 dramatically induce both proliferation and inhibition of apoptosis in vitro. We further provided evidence that in Hodgkin lymphoma Jagged1 is expressed in malignant as well as in bystander cells co-localizing with Notch-positive **tumor** cells. Notch signaling may therefore be activated in **tumor** cells by Jagged1 through homotypic or heterotypic cell-cell interactions and it seems likely that these interactions also contribute to lymphomagenesis in vivo. However, a pathogenetic role for Notch in multiple myeloma (MM), where

tight interactions between **neoplastic** plasma cells and their microenvironment are essential for **tumor** cell growth, is currently unknown. In this study, we therefore investigated Notch gene expression in cultured and primary multiple myeloma cells. To that end, we analyzed 14 cases of MM for expression of Notch1 and Notch2 by immunohistochemistry. In all cases Notch1 and Notch2 were highly expressed in MM cells. Strong Notch expression in MM cells was comparable to **tumor** cells of classic Hodgkin lymphoma, that we analyzed in our recent study. In contrast, we found low to undetectable levels of Notch1 and Notch2 in plasma cells of bone marrow of normal donors and in plasma cells of reactive lymphoid tissue. To verify high expression of Notch1 and Notch2 in cultured MM cells, we performed Western blot analysis of five MM cell lines. According to our data in primary MM cells, we found that both Notch receptors were highly expressed in all MM cell lines. However, freshly isolated CD19+ B cells and CD19+ B cells, that we differentiated to CD38+ plasmablastic cells in vitro, were almost completely devoid of Notch expression. Our data indicate that cultured and primary MM cells differ from their non-**neoplastic** counterparts with respect to strong Notch1 and Notch2 expression. Our data further provide evidence that ligand-induced Notch signaling is a novel growth factor for multiple myeloma cells and suggest that these interactions contribute to lymphomagenesis of multiple myeloma in vivo. Studies are under way to block Notch signaling by gamma-**secretase inhibitors** to further determine its role in **tumor** cell proliferation and resistance towards apoptosis in MM.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Molecular Genetics (Biochemistry and Molecular Biophysics); Oncology (Human Medicine, Medical Sciences)

IT Parts, Structures, & Systems of Organisms
bone marrow: blood and lymphatics, immune system; plasma cell: blood and lymphatics, immune system

IT Diseases
multiple myeloma: blood and lymphatic disease, immune system disease, **neoplastic** disease, genetics, therapy
Multiple Myeloma (MeSH)

IT Chemicals & Biochemicals
Notch1: signaling; Notch2: signaling

IT Miscellaneous Descriptors
heterotypic cell-cell interaction

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name

IT 403065-98-5 403065-99-6 403066-00-2 403066-01-3, 18: PN: WO0218544 SEQID: 1 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating the notch pathway)
IT 402941-23-5
RL: PRP (Properties)
(unclaimed sequence; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating the notch pathway)

L29 ANSWER 41 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:285458 BIOSIS
DOCUMENT NUMBER: PREV200200285458
TITLE: Structure-activity relationship of hydroxamate-based **inhibitors** on the **secretases** that cleave the amyloid precursor protein, angiotensin converting enzyme, CD23, and pro-**tumor** necrosis factor-alpha.
AUTHOR(S): Parkin, Edward T.; Trew, Alison; Christie, Gary; Faller, Andrew; Mayer, Ruth; Turner, Anthony J.; Hooper, Nigel M. [Reprint author]
CORPORATE SOURCE: Proteolysis Research Group, School of Biochemistry and Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK n.m.hooper@leeds.ac.uk
SOURCE: Biochemistry, (April 16, 2002) Vol. 41, No. 15, pp. 4972-4981. print.
CODEN: BICHAW. ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 May 2002
Last Updated on STN: 8 May 2002
AB Multiple proteins are proteolytically shed from the membrane, including the amyloid precursor protein (APP) involved in Alzheimer's disease, the blood pressure regulating angiotensin converting enzyme (ACE), the low affinity IgE receptor CD23, and the inflammatory cytokine **tumor** necrosis factor-alpha (TNF-alpha). The inhibitory effect of a range of hydroxamic acid-based compounds on the secretases involved in cleaving and releasing these four proteins has been examined to build up a structure-activity relationship. Compounds have been identified that can discriminate between TNF-alpha convertase and the other three secretases (compound 15), between the shedding of CD23 and the shedding of APP and ACE (compound 21), and between the secretases and matrix metalloproteinase-1 (compound 22). The structure-activity relationship for the APP alpha-secretase and the ACE secretase were remarkably similar, and both secretases were activated in whole cell systems by the serine proteinase inhibitor 3,4-dichloroisocoumarin. The basal and carbachol-stimulated shedding of APP and ACE from human SH-SY5Y neuroblastoma cells could not be differentiated by any of the hydroxamate compounds, implying that the same or very similar activities are involved in the constitutive and regulated shedding of these two proteins. By utilizing a key discriminatory compound (compound 15) that potently inhibits TNF-alpha convertase but not alpha-secretase, we show that TNF-alpha convertase is not involved in the regulated shedding of APP from human neuronal cells. The compounds reported here will be useful in future studies aimed at identifying and validating candidate secretases.
CC Cytology - General 02502
Cytology - Human 02508

Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
3,4-dichloroisocoumarin; CD23: cleavage; amyloid precursor protein: cleavage; angiotensin-converting enzyme [EC 3.4.15.1]: cleavage; carbachol; convertase; hydroxamate-based inhibitors: quantitative structure-activity relationships; matrix metalloproteinase-1 [MMP-1] [EC 3.4.24.7]; pro-**tumor** necrosis factor-alpha: cleavage; **secretase**: activity, **inhibition**
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
SH-SY5Y cell line: human neuroblastoma cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 51050-59-0 (3,4-dichloroisocoumarin)
9015-82-1 (angiotensin-converting enzyme)
9015-82-1 (EC 3.4.15.1)
51-83-2 (carbachol)
9001-12-1 (matrix metalloproteinase-1)
9001-12-1 (MMP-1)
9001-12-1 (EC 3.4.24.7)

L29 ANSWER 43 OF 55 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2002457787 EMBASE
TITLE: New treatment option for postmenopausal women with breasr cancer.
SOURCE: Expert Review of Anticancer Therapy, (2002) 2/6 (617-621).
ISSN: 1473-7140 CODEN: ERATBJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
CT Medical Descriptors:
*breast cancer: DT, drug therapy
*breast cancer: SU, surgery
*breast cancer: TH, therapy
*postmenopause
breast surgery
drug mechanism
thromboembolism: SI, side effect
endometrium cancer: SI, side effect
vein thrombosis: SI, side effect
hot flush: SI, side effect
kidney carcinoma: DT, drug therapy
cancer survival
survival time
optimal drug dose
lung non small cell cancer: DT, drug therapy
drug safety

stomach cancer: DT, drug therapy
pancreas cancer: DT, drug therapy
drug efficacy
antineoplastic activity
melanoma: DT, drug therapy
viral gene delivery system
head and neck cancer: DT, drug therapy
head and neck cancer: TH, therapy
skin ulcer: DT, drug therapy
skin ulcer: PC, prevention
skin ulcer: SI, side effect
chronic myeloid leukemia: DT, drug therapy
blood toxicity: SI, side effect
neutropenia: SI, side effect
human
nonhuman
female
note
Drug Descriptors:
anastrozole: AE, adverse drug reaction
anastrozole: CB, drug combination
anastrozole: CM, drug comparison
anastrozole: DT, drug therapy
anastrozole: PD, pharmacology
tamoxifen: AE, adverse drug reaction
tamoxifen: CB, drug combination
tamoxifen: CM, drug comparison
tamoxifen: DT, drug therapy
tamoxifen: PD, pharmacology
gamma secretase: EC, endogenous compound
aromatase inhibitor: DV, drug development
aromatase inhibitor: PD, pharmacology
Ras protein: EC, endogenous compound
protein Notch: EC, endogenous compound
yttrium 90
pemtumomab: CM, drug comparison
pemtumomab: PD, pharmacology
therafab: DV, drug development
therafab: DT, drug therapy
therex: DV, drug development
therex: DT, drug therapy
monoclonal antibody: CM, drug comparison
monoclonal antibody: DV, drug development
monoclonal antibody: DT, drug therapy
monoclonal antibody: PD, pharmacology
rituximab
capecitabine
trastuzumab
ae 941: DO, drug dose
ae 941: DT, drug therapy
ae 941: PD, pharmacology
mitozytrex: CB, drug combination
mitozytrex: DT, drug therapy
mitozytrex: PD, pharmacology
mitomycin derivative: CB, drug combination
mitomycin derivative: DT, drug therapy
mitomycin derivative: PD, pharmacology
patrin 2: DV, drug development
patrin 2: DT, drug therapy
patrin 2: PD, pharmacology

antineoplastic agent: AE, adverse drug reaction
antineoplastic agent: CB, drug combination
antineoplastic agent: DV, drug development
antineoplastic agent: DT, drug therapy
antineoplastic agent: PD, pharmacology
estradiol 3 methyl ether: DT, drug therapy
estradiol 3 methyl ether: PD, pharmacology
protein p53: DT, drug therapy
protein p53: PD, pharmacology
gene product: EC, endogenous compound
cancer vaccine: DT, drug therapy
cancer vaccine: PD, pharmacology
imatinib: AE, adverse drug reaction
imatinib: CB, drug combination
imatinib: CM, drug comparison
imatinib: DT, drug therapy
imatinib: PD, pharmacology
5 aza 2' deoxycytidine: AE, adverse drug reaction
5 aza 2' deoxycytidine: CB, drug combination
5 aza 2' deoxycytidine: CM, drug comparison
5 aza 2' deoxycytidine: DT, drug therapy
5 aza 2' deoxycytidine: PD, pharmacology
histone deacetylase inhibitor: CB, drug combination
histone deacetylase inhibitor: CM, drug comparison
histone deacetylase inhibitor: DT, drug therapy
histone deacetylase inhibitor: PD, pharmacology
topotecan: DT, drug therapy
topotecan: PD, pharmacology
DNA topoisomerase: EC, endogenous compound
camptothecin derivative: DT, drug therapy
camptothecin derivative: PD, pharmacology
unindexed drug
unclassified drug
mitoextra
advexin

RN (anastrozole) 120511-73-1; (tamoxifen) 10540-29-1; (yttrium 90) 10098-91-6; (rituximab) 174722-31-7; (capecitabine) 154361-50-9; (trastuzumab) 180288-69-1; (estradiol 3 methyl ether) 1035-77-4; (imatinib) 152459-95-5, 220127-57-1; (5 aza 2' deoxycytidine) 2353-33-5; (topotecan) 119413-54-6, 123948-87-8; (DNA topoisomerase) 80449-01-0

CN (1) Arimidex; (2) Pemtumomab; (3) Mabthera; (4) Xeloda; (5) Herceptin; (6) Neovastat; (7) Mitoextra; (8) Patrin 2; (9) Advexin; (10) Gleevec

CO (1) Astra Zeneca (United Kingdom); (5) Hoffmann La Roche (Switzerland); (6) Aeterna (Canada); (7) Supergen (United States); (8) KuDOS Pharmaceuticals (United Kingdom); (9) Introgen (United States); (10) Novartis (Switzerland); Genzyme (United States)

L29 ANSWER 45 OF 55 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:623023 HCAPLUS
DOCUMENT NUMBER: 137:292855
TITLE: Generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity
AUTHOR(S): Beher, Dirk; Wrigley, Jonathan D. J.; Owens, Andrew P.; Shearman, Mark S.
CORPORATE SOURCE: Departments of Biochemistry & Molecular Biology, Merck Sharp and Dohme Research Laboratories, Essex, CM20 2QR, UK
SOURCE: Journal of Neurochemistry (2002), 82(3), 563-575
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aberrant production of amyloid-β peptides by processing of the β-amyloid precursor protein (βAPP) leads to the **formation** of characteristic extracellular protein deposits which are thought to be cause of Alzheimer's disease. Therefore, inhibiting the key enzymes responsible for amyloid-β peptide generation, β- and γ- **secretase** may offer an opportunity to intervene with the progression of the disease. In human brain and cell culture systems a heterogeneous population of amyloid-β peptides with various truncations is detected and at present, it is unclear how they are produced. We have used a combination of surface enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS) and a specific **inhibitor** of γ- **secretase** to investigate whether the production of all amyloid-β peptide species requires the action of γ- **secretase.** Using this approach, we demonstrate that the production of all truncated amyloid-β peptides except those released by the action of the non-amyloidogenic α- **secretase** enzyme or potentially beta-site βAPP cleaving enzyme 2 depends on γ- **secretase** activity. This indicates that none of these peptides are generated by a sep. enzyme entity and a specific inhibitor of the γ- **secretase** enzyme should have the potential to block the generation of all amyloidogenic peptides. Furthermore in the presence of γ- **secretase** **inhibitors**, the observation of increased cleavage of the membrane-bound βAPP C-terminal fragment C99 by α- **secretase** suggests that during its trafficking C99 encounters compartments in which α- **secretase** activity resides.
CC 14-10 (Mammalian Pathological Biochemistry)
ST truncated amyloid beta peptide dependent gamma **secretase** Alzheimer disease; gamma **secretase** **inhibitor** may block generation amyloidogenic peptide
IT Protein motifs
(C-terminal fragment C99, of βAPP; generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity)
IT Amyloid precursor proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C-terminal fragment C99; generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity)
IT Alzheimer's disease
Human
(generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity)
IT Kidney
(human embryonic kidney HEK-293 cells; generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity)
IT Nerve, **neoplasm**
(neuroblastoma, human neuroblastoma SH-SY5Y cells; generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity)
IT Amyloid
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(β-, peptides, **formation**; generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity)

IT 338454-52-7, γ- **Secretase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; generation of C-terminally truncated amyloid-β peptides is dependent on γ- **secretase** activity)
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 47 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:315220 BIOSIS
DOCUMENT NUMBER: PREV200300315220
TITLE: GAMMA - **SECRETASE INHIBITORS** BIND REVERSIBLY TO THE ENZYME AND TARGET PRESENILINS.
AUTHOR(S): Clarke, E. E. [Reprint Author]; Wrigley, J. D. [Reprint Author]; Churcher, I.; Harrison, T.; Pollack, S. [Reprint Author]; Shearman, M. S. [Reprint Author]; Beher, D. [Reprint Author]
CORPORATE SOURCE: Biochemistry and Molecular Biology, Merck Sharp and Dohme, Harlow, UK
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 593.12. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jul 2003
Last Updated on STN: 9 Jul 2003

AB Proteolytic processing of the beta-amyloid precursor protein (APP) by a membrane bound aspartyl protease termed beta-site APP cleaving enzyme (BACE), generates a 99 amino acid membrane-bound C-terminal fragment. This in turn appears to be cleaved in the center of its transmembrane domain by gamma-secretase, producing amyloid-beta (A-beta) peptides. Since subsequent extracellular deposition of A-beta peptides in parenchymal senile plaques is a hallmark of Alzheimer's disease (AD) aberrant amyloid peptide production may represent a key step in the disease pathogenesis. Recent biochemical studies have established a close association between presenilin 1 and presenilin 2 (PS1/2) and the identity of gamma-secretase. To characterize the interactions of gamma-**secretase inhibitors** with the enzyme in membranes prepared from human SH-SY5Y neuroblastoma cells we have established a filtration-based radioligand binding assay. We were able to demonstrate that binding of a tritiated gamma-**secretase inhibitor** (KD =315pM) was specific and saturable, reaching a maximum binding of 1.5 pmol/mg membrane protein. Detailed analysis of inhibitor association and dissociation kinetics demonstrated reversible binding of the radioligand to the enzyme. Gamma-**secretase inhibitors** of different structural classes displaced the radioligand binding to membranes and furthermore the covalent labelling of a photoprobe to solubilized PS1. Taken together these data provide evidence that these inhibitors bind reversibly to the same or overlapping binding sites on PS1.

CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - Proteins, peptides and amino acids 10064
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506

Neoplasms - Pathology, clinical aspects and systemic effects 24004
IT Major Concepts
Nervous System (Neural Coordination)
IT Diseases
neuroblastoma: **neoplastic** disease, nervous system disease
Neuroblastoma (MeSH)
IT Chemicals & Biochemicals
amyloid-beta peptide: deposition; aspartyl protease [EC 3.4.23.16];
beta-amyloid precursor protein: proteolytic processing;
gamma-secretase: transmembrane domain, regulation; gamma-**secretase inhibitor**: enzyme **inhibitor**-drug;
presenilin 1 [PS1]; presenilin 2 [PS2]
IT Methods & Equipment
filtration-based radioligand binding assay: laboratory techniques
IT Miscellaneous Descriptors
dissociation kinetics; inhibitor association
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
SH-SY5Y cell line (cell line): human neuroblastoma cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 78169-47-8 (aspartyl protease)
144114-21-6 (aspartyl protease)
78169-47-8 (EC 3.4.23.16)
144114-21-6 (EC 3.4.23.16)
338454-52-7 (gamma-secretase)

L29 ANSWER 49 OF 55 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-098049 [13] WPIX
DOC. NO. CPI: C2002-030599
TITLE: New pyridine containing compounds useful as 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor in the treatment of e.g. cholesterol-related diseases.
DERWENT CLASS: B02
INVENTOR(S): CHEN, B; ROBL, J A; SUN, C; ROBI, J A
PATENT ASSIGNEE(S): (CHEN-I) CHEN B; (ROBL-I) ROBL J A; (SUNC-I) SUN C; (BRIM) BRISTOL-MYERS SQUIBB CO
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001096347	A1	20011220	(200213)*	EN	106
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
US 2002013334	A1	20020131	(200216)		
AU 2001066858	A	20011224	(200227)		
US 2002094977	A1	20020718	(200254)		
NO 2002006012	A	20030203	(200322)		
EP 1294728	A1	20030326	(200323)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
CZ 2002003930	A3	20030312	(200324)		

KR 2003036225	A	20030509 (200358)	
US 6627636	B2	20030930 (200367)	
CN 1436192	A	20030813 (200373)	
JP 2004503557	W	20040205 (200412)	177
HU 2003002937	A2	20031229 (200413)	
MX 2002012252	A1	20030601 (200417)	
US 2004092573	A1	20040513 (200432)	
ZA 2002010103	A	20040526 (200438)	111
US 6812345	B2	20041102 (200472)	
NZ 523627	A	20041029 (200474)	

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001096347	A1		WO 2001-US18864	20010612
US 2002013334	A1	Provisional	US 2000-211595P	20000615
			US 2001-875155	20010606
AU 2001066858	A		AU 2001-66858	20010612
US 2002094977	A1	Provisional	US 2000-211595P	20000615
		CIP of	US 2001-875155	20010606
			US 2001-7407	20011204
NO 2002006012	A		WO 2001-US18864	20010612
			NO 2002-6012	20021213
EP 1294728	A1		EP 2001-944447	20010612
			WO 2001-US18864	20010612
CZ 2002003930	A3		WO 2001-US18864	20010612
			CZ 2002-3930	20010612
KR 2003036225	A		KR 2002-717086	20021214
US 6627636	B2	Provisional	US 2000-211595P	20000615
		CIP of	US 2001-875155	20010606
			US 2001-7407	20011204
CN 1436192	A		CN 2001-811211	20010612
JP 2004503557	W		WO 2001-US18864	20010612
			JP 2002-510488	20010612
HU 2003002937	A2		WO 2001-US18864	20010612
			HU 2003-2937	20010612
MX 2002012252	A1		WO 2001-US18864	20010612
			MX 2002-12252	20021211
US 2004092573	A1	Provisional	US 2000-211595P	20000615
		CIP of	US 2001-875155	20010606
			US 2003-602752	20030624
ZA 2002010103	A		ZA 2002-10103	20021212
US 6812345	B2	Provisional	US 2000-211595P	20000615
		CIP of	US 2001-875155	20010606
		Div ex	US 2001-7407	20011204
			US 2003-602752	20030624
NZ 523627	A		NZ 2001-523627	20010612
			WO 2001-US18864	20010612

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001066858	A	Based on	WO 2001096347
EP 1294728	A1	Based on	WO 2001096347
CZ 2002003930	A3	Based on	WO 2001096347
JP 2004503557	W	Based on	WO 2001096347
HU 2003002937	A2	Based on	WO 2001096347
MX 2002012252	A1	Based on	WO 2001096347

US 6812345 B2 Div ex US 6627636
NZ 523627 A Based on WO 2001096347

PRIORITY APPLN. INFO: US 2000-211595P 20000615; US
2001-875155 20010606; US
2001-7407 20011204; US
2003-602752 20030624

AN 2002-098049 [13] WPIX

AB WO 200196347 A UPAB: 20020226

NOVELTY - Pyridine-containing compounds (I) are new.

DETAILED DESCRIPTION - Pyridine-containing compounds of formula (I), their salts (where R3 is H), ester, prodrug ester and stereosisomer are new.

X = O, S, or NR7;

Z' = -CH(OH)-CH2-C(R8)(OH)-CH2-CO2R3 or a group of formula (i);

asterisk = attachment point;

n = 0 or 1;

R1 and R2 = alkyl, aryalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;

R3 and R8 = H or lower alkyl;

R4 = H, halo, CF3, hydroxy, alkyl, alkoxy, alkanoylamino, aroylamino, or cyano;

R7 = H, alkyl, aryl, alkanoyl, aroyl, or alkoxycarbonyl;

R9 and R10 = H or alkyl;

R9+R10 = 3 - 7 membered carbocyclic ring;

dashed line = cis or trans single or double bond.

INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical combination comprising (I) and at least one hypolipidemic agent (1), lipid-lowering agent (2), lipid agent (3), lipid modulating agent (4), at least one other type of therapeutic agent (5) including antidiabetic agent (6), anti-obesity agent (7), antihypertensive agent (8), platelet aggregation inhibitor (9), anti-dementia agent (10), anti-Alzheimer's agent (11), antiosteoporosis agent (12), and/or hormone replacement therapeutic agent (13), other cardiovascular agent (14) including anti-anginal agent (15), anti-arrhythmic agent (16), anti-atherosclerosis agent (17), anti-inflammatory agent (18), anti-arthritis agent (19), anti-platelet agent (20), anti-heart failure agent (21)), anti-cancer agent (22), anti-infective agent (23), hormone replacement agent (24), growth hormone secretagogues (25), selective androgen receptor modulator (26), and/or immunomodulatory agent (27); and

(2) an intermediate of formula (II).

Q = -CO2T, CH2OH, -CH2-halide, -CH2-P(=O)(W)-W or a group of formula (ii);

T = alkyl; and

W = aryl, alkyl or alkoxy.

ACTIVITY - Antilipemic; Antiarteriosclerotic; Nootropic; Neuroprotective; Osteopathic; Cerebroprotective; Cardiant; Antiangial; Hypotensive; Antidiabetic; Anorectic; Cytostatic; Antiinflammatory; Litholytic; Hepatotropic; Anti-HIV; Antipsoriatic; Antiarrhythmic; Vasotropic; Anorectic.

MECHANISM OF ACTION - 3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor.

USE - (I) are used for inhibiting cholesterol biosynthesis or lowering blood serum cholesterol levels and/or modulating blood serum cholesterol levels, lowering low density lipoprotein (LDL) cholesterol and/or increasing high density lipoprotein (HDL) cholesterol, or treating dyslipidemia, mixed dyslipidemia, LDL Pattern B, LDL Pattern A, hyperlipidemia, hypercholesterolemia, hypo alpha -lipoproteinemia, hyperlipoproteinemia or hypertriglyceridemia, and other aberrations of apolipoprotein B metabolism, reducing levels of Lp(a); treating or

preventing other cholesterol-related diseases; treating, preventing or reversing progression of atherosclerosis, Alzheimer's disease, osteoporosis, osteopenia; reducing inflammatory markers, reducing C-reactive protein, or preventing or treating low grade vascular inflammation, stroke, dementia, coronary heart disease, primary and secondary prevention of myocardial infarction, stable and unstable angina, primary prevention of coronary events, secondary prevention of cardiovascular events, peripheral vascular disease, peripheral arterial disease, acute vascular syndromes, reducing the risk of undergoing myocardial revascularization procedure, microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome, hypertension, Type I and 2 diabetes and related diseases, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, Syndrome X, diabetic complications, dysmetabolic syndrome, and related diseases, and sexual dysfunction, malignant lesions, premalignant lesions, gastrointestinal malignancies, liposarcomas and epithelial **tumors**, cancer induced asthenia (fatigue), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and gall stones, and HIV infection, drug-induced lipodystrophy, proliferative diseases such as psoriasis, improving coagulation homeostasis, reducing PAI-1 activity, reducing fibrinogen, and/or reducing platelet aggregation, and/or improving endothelial function, cerebrovascular diseases (all claimed). Dwg.0/0

L29 ANSWER 51 OF 55 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-357642 [38] WPIX
DOC. NO. CPI: C2001-111042
TITLE: Alpha-sulfonylamino hydroxamic acid inhibitors of matrix metallo-proteinases, useful for treating peripheral or central nervous system disorders, e.g. Alzheimer's disease, multiple sclerosis, Huntington's disease and AIDS.
DERWENT CLASS: B03 B05
INVENTOR(S): SAHAGAN, B G; VILLALOBOS, A
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC; (PFIZ) PFIZER INC
COUNTRY COUNT: 32
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1088550	A1	20010404	(200138)*	EN	26
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
AU 2000061307	A	20010405	(200138)		
CA 2321593	A1	20010401	(200138)	EN	
JP 2001097854	A	20010410	(200138)		30
KR 2001050798	A	20010625	(200172)		
HU 2000003863	A2	20011228	(200216)		
ZA 2000005217	A	20020626	(200251)		47
US 6417229	B1	20020709	(200253)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1088550	A1	EP 2000-308442	20000927
AU 2000061307	A	AU 2000-61307	20000926
CA 2321593	A1	CA 2000-2321593	20000929
JP 2001097854	A	JP 2000-298071	20000929
KR 2001050798	A	KR 2000-57730	20000930

HU 2000003863	A2	HU 2000-3863	20000929
ZA 2000005217	A	ZA 2000-5217	20000928
US 6417229	B1 Provisional	US 1999-157083P	19991001
		US 2000-671435	20000927

PRIORITY APPLN. INFO: US 1999-157083P 19991001; US 2000-671435 20000927

AN 2001-357642 [38] WPIX

AB EP 1088550 A UPAB: 20010711

NOVELTY - Use of alpha-sulfonylamino hydroxamic acid derivatives (I) or their salts in the manufacture of a medicament for the treatment of a disease, condition or disorder of the peripheral or central nervous system, e.g. Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, Huntington's disease, Parkinson's disease, AIDS and prion diseases, is new.

DETAILED DESCRIPTION - The use of alpha-sulfonylamino hydroxamic acid derivatives of formula (I) or their salts of (I) in the manufacture of a medicament for the treatment in a mammal of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related cognitive decline, mild cognitive impairment and prion diseases, is new.

A = H or (CH2)n-(C=O)-Z;

n = 1-6;

Z = OH, 1-6C alkoxy or NR1R2;

R1R2 = e.g. H, 1-6C alkyl, piperidyl, 1-6C alkylpiperidyl, 6-10C arylpiperidyl, 2-9C heteroarylpiperidyl, 6-10C aryl-(1-6C alkylpiperidyl), 2-9C heteroaryl-(1-6C alkylpiperidyl), 1-6C acylpiperidyl, 6-10C aryl, 2-9C heteroaryl, 6-10C aryl-(1-6C alkyl), 2-9C heteroaryl-(1-6C alkyl), 6-10C aryl-(6-10C aryl), 6-10C aryl-(6-10C aryl)-(1-6C alkyl), 3-6C cycloalkyl, 3-6C cycloalkyl-(1-6C alkyl), R5(2-6 C alkyl) or 1-5C alkyl-(CHR3)-(1-6C alkyl);

R3 = OH, 1-6C acyloxy, 1-6C alkoxy, piperazino, 1-6C acylamino, 1-6C alkylthio, 6-10C arylthio, 1-6C alkylsulfinyl, 6-10C arylsulfinyl, 1-6C alkylsulfoxyl, 6-10C arylsulfoxyl, amino, 1-6C alkylamino, (1-6C alkyl)2amino, 1-6C acylpiperazino, 1-6C alkylpiperazino, 6-10C aryl-(1-6C alkylpiperazino), 2-9C heteroaryl-(1-6 C alkylpiperazino), morpholino, thiomorpholino, piperidino, pyrrolidino, R4(1-6 C alkyl) or 1-5C alkyl-(CHR4)-(1-6C alkyl);

R4 = piperidinyl, 1-6C alkylpiperidyl, 6-10C arylpiperidyl, 6-10C aryl-(1-6C alkylpiperidyl), 2-9C heteroarylpiperidyl, 2-9C heteroaryl-(1-6C alkylpiperidyl) or CH(R5)COR6;

R5 = H, 1-6C alkyl, 6-10C aryl-(1-6C alkyl), 2-9C heteroaryl-(1-6 C alkyl), 1-6C alkylthio-(1-6C alkyl), 6-10C arylthio-(1-6 C alkyl), 1-6C alkylsulfinyl-(1-6 C alkyl), 6-10C arylsulfinyl-(1-6 C alkyl), 1-6C alkylsulfonyl-(1-6 C alkyl), 6-10C arylsulfinyl-(1-6 C alkyl), hydroxy-(1-6C alkyl), amino(1-6C alkyl), 1-6 C alkylamino-(1-6C alkyl), (1-6 C alkylamino)2-(1-6 C alkyl), R7R8NCO-(1-6C alkyl) or R7OCO-(1-6C alkyl;

R7, R8 = H, 1-6C alkyl, 6-10C aryl-(1-6 C alkyl) or 2-9C heteroaryl-(1-6C alkyl);

R6 = R9R10N; and

R9, R10 = H, 1-6C alkyl, 6-10C aryl-(1-6C alkyl) or 2-9C heteroaryl-(1-6 C alkyl).

Full definitions are given in the Definitions Field.

An INDEPENDENT CLAIM is included for the use of a prodrug of formula (II) in the manufacture of a medicament for the treatment of a disease,

condition or disorder in the peripheral or central nervous system, including Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal chord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS (acquired immune deficiency syndrome), age-related cognitive decline, mild cognitive impairment and prion diseases.

X1, X2 = 1-6C alkyl or X1 + X2 together with the atom to which they are attached form a ring selected from 5-7C cycloalkyl, 4-tetrahydropyranyl or 4-piperidinyl;

Y = a substituent on a phenyl ring carbon which is capable of supporting an additional bond, preferably 1-2 substituents, especially 1 substituent, most especially 1 substituent at the 4-position on the phenyl ring, selected from H, F, Cl, CF3, 1-6C alkoxy, trifluoromethoxy, difluoromethoxy or 1-6C alkyl;

U, V = carbonyl, methylene (optionally substituted by OH), SO2 or SO3; and

b = 1-3.

ACTIVITY - Nootropic; neuroprotective; cerebroprotective; vasotropic; antiparkinsonian; antimigraine; antiHIV; anticonvulsant; vasotropic.

MECHANISM OF ACTION - (I) and prodrugs of (I) are inhibitors of mammalian reprolysin and/or of matrix metallo-proteinases (including MMP-2 and MMP-9).

The compounds (I) were incubated in a suspension of human monocytes for 4 hours at 37 deg. C in a humidified carbon dioxide incubator. The plates were then removed and centrifuged and the supernatants removed and assayed for TNF- alpha (**tumor** necrosis factor-alpha) using an ELIZA assay. (I) were found to possess selective activity against MMP-2 and MMP-9 and to have IC50 values of less than 500 nM against either or both of MMP-2 and MMP-9.

USE - The sulfonamide derivatives (I) are useful for treating diseases, conditions or disorders in the peripheral or central nervous system, including Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal chord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS (acquired immune deficiency syndrome), age-related cognitive decline, mild cognitive impairment and prion diseases. (I) is also useful in the manufacture of a medicament combined with a non-steroidal anti-inflammatory drug for the treatment of the diseases listed above. The sulfonamide prodrug (II) is useful in the preparation of a medicament for the treatment of the diseases listed above (all claimed). Further diseases, conditions and disorders are disclosed.
Dwg.0/0

L29 ANSWER 53 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:165443 BIOSIS
DOCUMENT NUMBER: PREV200200165443
TITLE: gamma-Secretase-dependent cleavage and nuclear localization of the ErbB-4 receptor tyrosine kinase.
AUTHOR(S): Ni, Chang-Yuan [Reprint author]; Murphy, Michael Paul; Golde, Todd E.; Carpenter, Graham [Reprint author]
CORPORATE SOURCE: Biochemistry, Vanderbilt University School of Medicine, 21st Ave South, 639 Light Hall, Nashville, TN, 37232, USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 329a. print.
Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology. Washington DC, USA. December 08-12, 2001. American Society for Cell Biology.
CODEN: MBCEEV. ISSN: 1059-1524.
DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Mar 2002
Last Updated on STN: 5 Mar 2002
CC General biology - Symposia, transactions and proceedings 00520
Cytology - General 02502
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics)
IT Parts, Structures, & Systems of Organisms
cytosol; nucleus
IT Chemicals & Biochemicals
ErbB-4: cleavage, nuclear localization, proteolytic processing, type I transmembrane receptor tyrosine kinase; Notch: non-tyrosine kinase transmembrane receptor; TACE [**tumor** necrosis factor-alpha converting enzyme]: transmembrane metalloprotease; TPA [tissue plasminogen activator]; cytoplasmic domain fragment; ectodomain fragment; gamma-secretase; gamma-**secretase inhibitors** : enzyme **inhibitor**-drug; heregulin; presenilin-1; receptor tyrosine kinase domain
IT Miscellaneous Descriptors
signal transduction; Meeting Abstract
RN 338454-52-7 (gamma-secretase)
139639-23-9 (TISSUE PLASMINOGEN ACTIVATOR)
151769-16-3 (**TUMOR** NECROSIS FACTOR-ALPHA CONVERTING ENZYME)
158736-49-3 (GAMMA-SECRETASE)

L29 ANSWER 55 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1996:182061 BIOSIS
DOCUMENT NUMBER: PREV199698738190
TITLE: Shedding of the lymphocyte L-selectin adhesion molecule is inhibited by a hydroxamic acid based protease inhibitor: Identification with an L-selectin-alkaline phosphatase reporter.
AUTHOR(S): Feehan, Carol; Darlak, Krzysztof; Kahn, Julius; Walcheck, Bruce; Spatola, Arno F.; Kishimoto, Takashi Kei [Reprint author]
CORPORATE SOURCE: Boehringer Ingelheim Pharmaceuticals, Dep. Immunological Diseases R6-5, 900 Ridgebury Road, Box 368, Ridgefield, CT 06877, USA
SOURCE: Journal of Biological Chemistry, (1996) Vol. 271, No. 12, pp. 7019-7024.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Apr 1996
Last Updated on STN: 29 Apr 1996
AB Expression of the L-selectin adhesion molecule can be rapidly down-modulated by regulated proteolysis at a membrane-proximal site. The L-selectin secretase has remained undefined, and the secretase activity is resistant to a broad panel of common protease inhibitors. We have developed an L-selectin-alkaline phosphatase reporter, consisting of the ectodomain of human placental alkaline phosphatase fused to the membrane-proximal cleavage, transmembrane, and cytoplasmic domains of L-selectin, to aid in the screening for L-selectin **secretase inhibitors.** A hydroxamic acid-based metalloprotease inhibitor, KD-IX-73-4, inhibited release of the L-selectin-alkaline phosphatase reporter in a dose-dependent manner. The hydroxamic acid-based peptide

was also found to inhibit wild type L-selectin down-regulation from the surfaces of phorbol myristate acetate-activated peripheral blood lymphocytes and phytohemagglutinin-stimulated lymphoblasts. Analysis of the proteolytic cleavage fragments of L-selectin confirmed that KD-IX-73-4 inhibited L-selectin proteolysis. Lymphocyte L-selectin was not down-regulated when co-cultured with formylmethionylleucylphenylalanine-stimulated neutrophils, suggesting that the putative secretase acts in cis with the membrane-bound L-selectin. These results suggest that the L-selectin secretase activity may involve a cell surface, zinc-dependent metalloprotease, although L-selectin shedding is not affected by EDTA and may be related to the recently described activity involved in processing of membrane-bound TNF-alpha.

CC Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Minerals 10069
Biophysics - Molecular properties and macromolecules 10506
Enzymes - Chemical and physical 10806
Blood - Blood cell studies 15004
Blood - Lymphatic tissue and reticuloendothelial system 15008
Endocrine - General 17002

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals
PROTEASE INHIBITOR; PHOSPHATASE; ZINC; METALLOPROTEASE

IT Miscellaneous Descriptors
ECTODOMAIN; KD-IX-73-4; L-SELECTIN SECRETASE; **TUMOR** NECROSIS FACTOR-ALPHA; ZINC-DEPENDENT METALLOPROTEASE

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 37205-61-1 (PROTEASE INHIBITOR)
9013-05-2 (PHOSPHATASE)
7440-66-6 (ZINC)
81669-70-7 (METALLOPROTEASE)

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human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
GEN human Notch1 gene (Hominidae): expression; human Notch2 gene (Hominidae): expression

L29 ANSWER 25 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:501642 BIOSIS
DOCUMENT NUMBER: PREV200300498078
TITLE: Synthesis of analogs of gamma-**secretase inhibitor.**
AUTHOR(S): Zhang, Xiaodong [Reprint Author]; Yin, Ye [Reprint Author]; Bornmann, William [Reprint Author]; Li, Yueming [Reprint Author]
CORPORATE SOURCE: Memorial Sloan Kettering Cancer Center, New York, NY, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 688. print. Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003
CC General biology - Symposia, transactions and proceedings 00520
Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
IT Major Concepts
Pharmacology; **Tumor** Biology
IT Diseases
cancer: **neoplastic** disease, therapy
Neoplasms (MeSH)
IT Chemicals & Biochemicals
L 685458: **antineoplastic**-drug, gamma-**secretase inhibitor**; gamma-**secretase inhibitors**: analog synthesis, **antitumor** activity
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
animal (common): animal model
Taxa Notes
Animals
RN 292632-98-5 (L 685458)

L29 ANSWER 27 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:539322 BIOSIS
DOCUMENT NUMBER: PREV200300541695
TITLE: Notch-1 mediated signaling increases IKKalpha levels: A critical determinant controlling keratinocyte terminal differentiation and cell survival.
AUTHOR(S): Chaturvedi, V. [Reprint Author]; Qin, J. [Reprint Author]; Denning, M. F. [Reprint Author]; Miele, L. [Reprint

Author]; Nickoloff, B. J. [Reprint Author]
CORPORATE SOURCE: Pathology, Loyola University Chicago, Maywood, IL, USA
SOURCE: Journal of Investigative Dermatology, (July 2003) Vol. 121, No. 1, pp. 0493. print.
Meeting Info.: International Investigative Dermatology 2003 : Joint Meeting of the European Society for Dermatological Research, Japanese Society for Investigative Dermatology and Society for Investigative Dermatology. Miami Beach, Florida, USA. April 30-May 04, 2003. European Society for Dermatological Research.
ISSN: 0022-202X (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Endocrine - General 17002
Integumentary system - Physiology and biochemistry 18504
IT Major Concepts
Biochemistry and Molecular Biophysics; Integumentary System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
epidermal layer; keratinocyte: integumentary system; mitochondria
IT Chemicals & Biochemicals
IFN-gamma [interferon-gamma]; IKK-alpha: endogenous, accumulation, regulation; Jagged-1; Notch-1: signaling; Notch-1 receptor; Notch-4 receptor; PKC-gamma; TNF-alpha [**tumor** necrosis factor-alpha]; caspase 3: activation; caspase inhibitor; cytochrome C: release; gamma-**secretase inhibitor**; involucrin-loricrin; p21
IT Miscellaneous Descriptors
apoptosis; cell differentiation; cell proliferation; cell survival; epidermopoiesis; growth arrest
RN 169592-56-7 (caspase 3)
9007-43-6 (cytochrome C)
GEN Hes-1 gene

L29 ANSWER 29 OF 55 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003223599 EMBASE
TITLE: The structural revolution.
AUTHOR: Verdonk M.
CORPORATE SOURCE: M. Verdonk, Astex Technology Ltd, 436 Cambridge Sci. Park, Milton Road, Cambridge CB4 0QA, United Kingdom.
m.verdonk@astex-technology.com
SOURCE: Current Drug Discovery, (1 May 2003) -/MAY (44-46).
ISSN: 1472-7463 CODEN: CDDUAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The increasing availability in recent years of 3D structures of protein targets and their co-crystals has enabled structure-guided drug design to become a revolutionary new tool for lead generation and optimization. Fragment-based screening using techniques such as NMR, X-ray and virtual screening are becoming more important daily.

CT Medical Descriptors:
*protein structure
*drug design
three dimensional imaging
protein targeting
crystal structure
X ray crystallography
drug screening
methodology
nuclear magnetic resonance
nuclear magnetic resonance spectroscopy
structure activity relation
drug industry
protein function
protein expression
protein purification
protein analysis
automation
antineoplastic activity
conference paper
Drug Descriptors:
synaptophysin: EC, endogenous compound
beta secretase: EC, endogenous compound
hydroxysteroid dehydrogenase: EC, endogenous compound
fatty acid binding protein: EC, endogenous compound
cyclooxygenase 2: EC, endogenous compound
estrogen receptor: EC, endogenous compound
thrombin: EC, endogenous compound
gelatinase A: EC, endogenous compound
sialidase: EC, endogenous compound
olomoucine: AN, drug analysis
olomoucine: CM, drug comparison
olomoucine: PD, pharmacology
carbonate dehydratase: EC, endogenous compound
stromelysin: EC, endogenous compound
matrix metalloproteinase inhibitor: AN, drug analysis
matrix metalloproteinase inhibitor: CM, drug comparison
neutrophil collagenase: EC, endogenous compound
cyclin dependent kinase inhibitor: AN, drug analysis
cyclin dependent kinase inhibitor: CM, drug comparison
cyclin dependent kinase inhibitor: DV, drug development
cyclin dependent kinase inhibitor: PD, pharmacology
nu 6102: AN, drug analysis
nu 6102: CM, drug comparison
nu 6102: DV, drug development
nu 6102: PD, pharmacology
unclassified drug

RN (hydroxysteroid dehydrogenase) 9001-56-3; (thrombin) 9002-04-4; (gelatinase A) 146480-35-5; (sialidase) 9001-67-6; (olomoucine) 101622-51-9; (carbonate dehydratase) 9001-03-0; (stromelysin) 79955-99-0

CO Astra Zeneca; Novartis; Schering Plough; Hoffmann La Roche

L29 ANSWER 31 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:203027 BIOSIS

DOCUMENT NUMBER: PREV200400203570
TITLE: p75!NTR regulated intramembrane proteolysis in Schwann cells.
AUTHOR(S): Zampieri, N. [Reprint Author]; Chao, M. V. [Reprint Author]
CORPORATE SOURCE: Skirball Inst. of BioMol. Med., NYU Sch. of Med., New York, NY, USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 677.11. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB Neurotrophins regulate neuronal survival and differentiation during development by using two different receptors classes, the Trk family of receptor tyrosine kinases (Trk A, B, and C) and the p75NTR receptor, a member of the **tumor** necrosis factor receptor superfamily. Regulated Intramembrane Proteolysis (RIP) has recently emerged as a conserved mechanism for controlling various signaling pathways. The process consists of the intramembrane proteolysis of transmembrane proteins releasing luminal/extracellular domains that can translocate to a new compartment where they can elicit their biological responses. Previously it was shown that p75NTR undergoes extracellular domain shedding (DiStefano PS et al., 1988, PNAS, 85:270-274). The resulting membrane bound C-terminal fragment can be subsequently cleaved by gamma-secretase activity to produce the cytoplasmic domain. This phenomenon was observed either in transfected cell lines (HEK293 and NIH3T3), PC12 cells, and in primary Schwann cells cultures. The production of the intracellular fragment can be selectively **inhibited** by gamma-**secretase inhibitors** (compound X and E), leading to the accumulation of the membrane-bound C-terminal fragment, which formation can be in turn blocked by using metalloproteases inhibitors (TAPI). Phorbol esters (PMA) have the opposite effect and activate metalloproteases increasing the levels of both the membrane-bound c-terminal fragment and of the intracellular domain. The regulation and consequences of p75NTR by gamma-secretase in Schwann cells are being followed.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - General 10060
Nervous system - Physiology and biochemistry 20504

IT Major Concepts
Nervous System (Neural Coordination)

IT Parts, Structures, & Systems of Organisms
Schwann cells: nervous system; cytoplasmic domain; membrane; transfected cells

IT Chemicals & Biochemicals
C-terminal fragment; PMA [phorbol ester]; RIP; TAPI; Trk; Trk A; gamma-secretase; gamma-**secretase inhibitor**; neurotrophin; p75NTR; receptor tyrosine kinases; transmembrane protein; **tumor** necrosis factor receptor

IT Miscellaneous Descriptors
regulated intramembrane proteolysis

ORGN Classifier
Muridae 86375
Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
PC12 cell line (cell line)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 62-38-4Q (PMA)
64-13-1Q (PMA)
16561-29-8Q (PMA)
25087-26-7Q (PMA)
78565-16-9Q (PMA)
276704-22-4Q (PMA)
62-38-4Q (phorbol ester)
64-13-1Q (phorbol ester)
16561-29-8Q (phorbol ester)
25087-26-7Q (phorbol ester)
78565-16-9Q (phorbol ester)
276704-22-4Q (phorbol ester)
338454-52-7 (gamma-secretase)
340830-03-7 (receptor tyrosine kinases)

L29 ANSWER 33 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:200685 BIOSIS
DOCUMENT NUMBER: PREV200400201243
TITLE: Gene expression changes consequent to pharmacological gamma - **secretase inhibition** in a neuroglioma cell line stably transfected with mutant amyloid precursor protein.
AUTHOR(S): Facchinetti, F. [Reprint Author]; D'Arrigo, A. [Reprint Author]; Aporti, C. [Reprint Author]; Nofrate, V. [Reprint Author]; Fabris, M. [Reprint Author]; del Giudice, E. [Reprint Author]; Bertola, A. [Reprint Author]; Leon, A. [Reprint Author]
CORPORATE SOURCE: Res.&Innovation, Padua, Italy
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 523.20. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004
AB One of the most promising therapeutic strategy in Alzheimer's disease (AD) involves approaches aiming to retard, halt, or prevent the formation or accumulation of amyloid-beta (Abeta) plaques. The most direct way of reducing Abeta production is through the **inhibition** of gamma-**secretase** which is one of the specific proteases that drives the peptide production. A class of compounds exemplified by N-(N-(3,5-difluorophenylacetyl)-L-alanyl)-S-phenylglycine t-butyl ester (DAPT) reduces Abeta production by selectively **inhibiting** gamma-**secretase** proteolytic activity both in vivo and in vitro. Although DAPT efficacy in reducing Abeta production is not associated to acute cellular toxicity, **inhibition** of gamma-**secretase** leads to accumulation of its substrate and the suppression of a 59-or 57-residue long carboxy terminal fragment (gamma-CTF) of APP. gamma-CTF has been shown to translocate into the nucleus, to modulate gene

expression and to play a role in physiologic intracellular signalling. Being gamma-secretase a potential therapeutic target in AD, it becomes important to understand the consequences of its pharmacological inhibition on the gene expression. By applying a gene microarray-based approach we are currently examining the changes of gene expression induced by treatment with DAPT in a neuroglioma cell line transfected with human APP (H4/APP) carrying familial AD-associated mutations. The results obtained with a customized array of PCR-amplified cDNA probes, representing approximately 5000 selected human genes, will be presented in detail. This approach may help to clarify the functional role of proteolytic APP processing.

CC General biology - Symposia, transactions and proceedings 00520
Genetics - General 03502
Genetics - Human 03508
Behavioral biology - Human behavior 07004
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Nervous System (Neural Coordination); Neurology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Psychiatry (Human Medicine, Medical Sciences)

IT Parts, Structures, & Systems of Organisms
neuroglioma cells: nervous system; plaques: nervous system

IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)

IT Diseases
familial AD: genetic disease, nervous system disease

IT Diseases
neuroglioma: **neoplastic** disease, nervous system disease

IT Chemicals & Biochemicals
DAPT; amyloid precursor protein; amyloid-beta; cDNA; gamma-CTF; gamma-secretase; genes; phenylglycine; protease [EC 3.4.21.62]

IT Methods & Equipment
gene microarray: genetic techniques, laboratory techniques

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 338454-52-7 (gamma-secretase)
103-01-5Q (phenylglycine)
2835-06-5Q (phenylglycine)
9001-92-7 (protease)
9014-01-1 (protease)
9001-92-7 (EC 3.4.21.62)
9014-01-1 (EC 3.4.21.62)

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ACCESSION NUMBER: 2004:197004 BIOSIS
DOCUMENT NUMBER: PREV200400197563
TITLE: Inhibition of Notch processing in a human T - cell lymphoma.
AUTHOR(S): Gadient, R. A. [Reprint Author]; Jiang, Q.; Tian, G.; Liu, F.; Greenberg, B. D.; Piser, T. M.
CORPORATE SOURCE: Dept. Neurosci, AstraZeneca Pharmaceut., Wilmington, DE, USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 295.1. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004
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AB Alzheimer's disease is the most prominent neurodegenerative disorder affecting a large percentage of the older human population. A key pathological hallmark is the presence of amyloid plaques in the entorinal cortex and the hippocampus. Beta amyloid, the main component of the plaques is formed from a much larger precursor by a series of proteolytic events. The terminal cleavage is controlled by gamma secretase, which is a multimeric protein complex consisting of at least four different proteins. In addition, gamma secretase has been shown to process a variety of different protein substrates among them APP and Notch. Gamma secretase cleavage of Notch is required to release the intracellular domain (NICD), which is a transcription factor important in regulating cell fate decisions in a variety of cell types including neurons and lymphocytes. As a consequence, **inhibition** of gamma **secretase** as a therapeutic approach for Alzheimer's disease has the potential to cause serious side effects by inhibiting the processing of other important molecules such as Notch. Therefore compounds aimed to inhibit the formation of beta amyloid must be screened for inhibition of other substrates. Here we focus on Notch processing in a human T cell lymphoma. This cell line produces substantial amounts of NICD. Exposure to gamma **secretase inhibitors blocked** the formation of NICD in a dose-dependent manner. Biochemical and molecular biological characterization of the cell line confirmed the presence of all four known components of the gamma secretase complex. In addition, a membrane preparation from these cells contained gamma secretase activity in vitro, which was also blocked in a dose-dependent manner by a known gamma **secretase inhibitor.** In summary, this cell line is a valuable tool for developing substrate selective **inhibitors** of gamma-**secretase.**

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Behavioral biology - Human behavior 07004
Biochemistry studies - Proteins, peptides and amino acids 10064
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004

Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Nervous System (Neural Coordination); Neurology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Psychiatry (Human Medicine, Medical Sciences)
IT Parts, Structures, & Systems of Organisms
T-cells: blood and lymphatics, immune system; amyloid plaques: nervous system; hippocampus: nervous system; lymphocytes: blood and lymphatics, immune system; membrane; neurons: nervous system; plaques: nervous system
IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)
IT Diseases
T-cell lymphoma: blood and lymphatic disease, immune system disease, **neoplastic** disease
Lymphoma, T-Cell (MeSH)
IT Diseases
neurodegenerative disorder: nervous system disease
Neurodegenerative Diseases (MeSH)
IT Chemicals & Biochemicals
NICD; Notch; amyloid; beta-amyloid; gamma secretase; gamma **secretase inhibitor**; gamma **secretase inhibitor**; gamma-secretase; protein complex; transcription factor
IT Miscellaneous Descriptors
Notch processing
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 338454-52-7 (gamma secretase)
338454-52-7 (gamma-secretase)

L29 ANSWER 37 OF 55 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:336050 BIOSIS
DOCUMENT NUMBER: PREV200200336050
TITLE: Amyloid-lowering isocoumarins are not direct **inhibitors** of gamma-**secretase.**
AUTHOR(S): Esler, William P. [Reprint author]; Das, Chittaranjan [Reprint author]; Campbell, William A. [Reprint author]; Kimberly, W. Taylor [Reprint author]; Kornilova, Anna Y. [Reprint author]; Diehl, Thekla S. [Reprint author]; Ye, Wenjuan [Reprint author]; Ostaszewski, Beth L. [Reprint author]; Xia, Weiming [Reprint author]; Selkoe, Dennis J. [Reprint author]; Wolfe, Michael S. [Reprint author]
CORPORATE SOURCE: Center for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA, 02115, USA
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SOURCE: Nature Cell Biology, (May, 2002) Vol. 4, No. 5, pp. E110-E111. print.
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CC Cytology - Animal 02506
Cytology - Human 02508
Behavioral biology - Human behavior 07004
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology

IT Parts, Structures, & Systems of Organisms
Golgi; brain: nervous system

IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)

IT Chemicals & Biochemicals
C100-Flag; DAPT: enzyme inhibitor-drug; JLK2; JLK6; Notch receptor; WPE-III-31C: enzyme inhibitor-drug; amyloid-beta precursor protein [APP]: expression; amyloid-beta protein: production; gamma-secretase; isocoumarin: enzyme inhibitor-drug; presenilin 1; presenilin 2

ORGN Classifier
Cricetidae 86310
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
CHO cell line: Chinese hamster ovary cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HeLa cell line: human cervical **cancer** cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 338454-52-7 (gamma-secretase)
491-31-6 (isocoumarin)

L29 ANSWER 39 OF 55 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:172048 HCAPLUS
DOCUMENT NUMBER: 136:229066
TITLE: Method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating the notch pathway
INVENTOR(S): Nickoloff, Brian J.; Miele, Lucio
PATENT ASSIGNEE(S): Loyola University Chicago, USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018544	A2	20020307	WO 2001-US27246	20010831
WO 2002018544	C2	20030403		
WO 2002018544	A3	20030612		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001088628	A5	20020313	AU 2001-88628	20010831
US 2002151487	A1	20021017	US 2001-944849	20010831
PRIORITY APPLN. INFO.:			US 2000-229614P P	20000831
			WO 2001-US27246 W	20010831

AB The invention concerns methods and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders. In one embodiment, the invention provides a method of inducing differentiation of an epithelial cell. In another embodiment, the invention provides a method for inducing **formation** of a barrier within epithelium. In another embodiment, the invention provides a method for producing differentiated epidermis. In another embodiment, the invention provides a method of assaying for genetic propensity of a patient to develop a disorder associated with epithelial barrier **formation.** In another embodiment, the invention provides a diagnostic test to determine the expression levels of Notch ligands. In another embodiment, the invention provides a method of preventing or retarding the progression of a benign or malignant disorder in skin.

IC ICM C12N005-00
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 1, 3, 14
ST Notch pathway differentiation diagnosis skin epithelium barrier **formation cancer**
IT Protein motifs
(Delta/Serrate/LAG-2; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Proteins
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Delta; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating

notch pathway)

IT Cell adhesion molecules
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(ICAM-1 (intercellular adhesion mol. 1); method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Proteins
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(JAG-1; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Proteins
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(JAG-2; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Proteins
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Jagged 1, as Notch ligands; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Proteins
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Jagged 2, as Notch ligands; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Proteins
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Lunatic-Fringe; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Proteins
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Manic-Fringe; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Transcription factors
RL: ANT (Analyte); ANST (Analytical study)
(NF-κB (nuclear factor of κ light chain gene enhancer in B-cells); method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Notch (receptor)
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Notch1; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Notch (receptor)
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Notch2; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating

notch pathway)
IT Notch (receptor)
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Notch3; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Notch (receptor)
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Notch4; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Ligands
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Notch; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Cell adhesion molecules
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(PECAM-1; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Proteins
RL: ANT (Analyte); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Radical Fringe; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Proteins
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Serrate; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Skin, **neoplasm**
(T-cell lymphoma; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Nucleotides, properties
RL: PRP (Properties)
(antisense; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Skin, **neoplasm**
(basal cell carcinoma; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Biological transport
(**carrier**-mediated; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Eye
(cornea; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)
IT Gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(expression, overexpression; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT DNA
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(genomic; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Proteins
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(hJagged 1; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Immunoassay
(immunoblotting; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Immunoassay
(immunohistochem.; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Skin
(keratinocyte; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Cell differentiation
Diagnosis
Digestive tract
Epithelium
Genetic methods
Immunoassay
Melanoma
Protein sequences
Respiratory tract
Signal transduction, biological
Skin, **neoplasm**
Susceptibility (genetic)
Urogenital tract
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT CD34 (antigen)
Cell adhesion molecules
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT DNA
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT RNA
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT cDNA

RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Antibodies and Immunoglobulins
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Notch (receptor)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Mouth
(mucosa; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Epithelium
(pre-malignant; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Carcinoma
(squamous cell; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT Skin
(stratum corneum; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT 219127-21-6 402941-20-2 402941-21-3 402941-22-4 403065-44-1
403065-45-2 403065-46-3 403065-47-4 403065-48-5 403065-49-6
403065-50-9
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(amino acid sequence; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT 403065-51-0 403065-52-1
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(amino acid sequence; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT 338454-52-7, γ- **Secretase**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitor** of; method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT 61869-41-8, Luciferase
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)

IT 141436-78-4, Protein kinase C 362516-16-3, IKKα kinase
362517-43-9, IKKβ kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method and reagents for epithelial barrier **formation** and treatment of malignant and benign skin disorders by modulating notch pathway)